

(0.10 mL, 0.85 mmol), and potassium carbonate (0.134 g, 0.97 mmol) in dimethylformamide (5 mL) at ambient temperature for 20 hours. The reaction mixture was diluted with water and the resulting precipitate was collected by filtration, and dried to give the title compound (0.165 g, 80%). MS (DCI/NH₃) m/z 277 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.21 (s, 2 H) 7.25 (d, J=5.52 Hz, 1 H) 7.35 (m, 5 H) 8.28 (d, J=5.52 Hz, 1 H).

Example 110C

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 110B for the product of Example 1B (0.137 g, 49%). MS (ESI-) m/z 438 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 5.26 (s, 2 H) 7.03 (d, J=5.52 Hz, 1 H) 7.21 (m, 2 H) 7.28 (m, 5 H) 7.54 (ddd, J=8.27, 7.17, 1.47 Hz, 1 H) 7.65 (dd, J=7.91, 1.29 Hz, 1 H) 7.73 (d, J=5.52 Hz, 1 H) 15.89 (s, 1 H).

Example 111

4-butyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

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Example 111A

1-butyl-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 110B substituting n-butyl bromide for benzyl bromide (0.059 g, 22%). MS (DCI) m/z 226 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 0.91 (t, J=7.17 Hz, 3 H) 1.36 (dt, J=22.70, 7.22 Hz, 2 H) 1.62 (m, 2 H) 3.94 (m, 2 H) 7.39 (d, J=5.52 Hz, 1 H) 8.34 (d, J=5.15 Hz, 1 H).

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Example 111B

4-butyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

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The title compound was prepared according to the procedure of Example 1D substituting the product of Example 111A for the product of Example 1B (0.050 g, 47%). MS (DCI/NH₃) m/z 404 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (m, 3 H) 1.40 (td, J=14.98, 7.17 Hz, 2 H) 1.67 (m, 2 H) 4.27 (m, 2 H) 7.54 (m, 1 H) 7.60 (d, J=5.52 Hz, 1 H) 7.67 (d, J=7.72 Hz, 1 H) 7.77 (ddd, J=8.36, 7.08, 1.47 Hz, 1 H) 7.92 (d, J=7.72 Hz, 1 H) 8.39 (d, J=5.52 Hz, 1 H) 14.46 (s, 1 H) 14.90 (s, 1 H).

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Example 112

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(4-pyridinylmethyl)thieno[3,2-b]pyridin-5(4H)-one

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Example 112A

1-(pyridin-4-ylmethyl)-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 4-bromomethyl pyridine hydrobromide for n-butyl bromide (0.205 g, 80%).

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Example 112B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(4-pyridinylmethyl)thieno[3,2-b]pyridin-5(4H)-one

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The title compound was prepared according to the procedure of Example 1D substituting the product of Example 112A for the product of Example 1B (0.155 g, 45%). MS (DCI/NH₃) m/z 439 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.78 (s, 2 H) 7.49 (d, J=5.52 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.62 (d, J=7.35 Hz, 1 H) 7.76 (m, 4 H) 7.93 (d, J=7.72 Hz, 1 H) 8.38 (d, J=5.52 Hz, 1 H) 8.75 (d, J=6.25 Hz, 1 H) 14.06 (s, 1 H).

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Example 113

1-(3-bromobenzyl)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6,7,8-tetrahydro-2(1H)-quinolinone

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Example 113A

5,6,7,8-tetrahydro-2H-3,1-benzoxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 3B substituting ethyl 2-aminocyclohex-1-ene-1-carboxylate for the product of Example 3A (0.960 g, 97%). MS (ESI-) m/z 166 (M-H)⁺.

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Example 113B

1-(3-bromobenzyl)-5,6,7,8-tetrahydro-2H-3,1-benzoxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 113A for the product of Example 1A and substituting 3-bromobenzyl bromide for n-butyl bromide (0.049 g, 46%).

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MS (ESI-) m/z 334 (M-H)⁺.

Example 113C

1-(3-bromobenzyl)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6,7,8-

tetrahydro-2(1H)-quinolinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 113B for the product of Example 1B (0.021 g, 34%). MS (ESI-) m/z 514 (M-H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 1.68 (m, 4 H), 2.51 (m, 2 H), 2.67 (m, 2 H), 5.40 (s, 2 H), 7.13 (d, $J=7.72$ Hz, 1 H), 7.30 (t, $J=7.91$ Hz, 1 H), 7.51 (m, 3 H), 7.61 (d, $J=8.09$ Hz, 1 H), 7.73 (t, $J=7.17$ Hz, 1 H), 7.90 (d, $J=8.46$ Hz, 1 H), 14.40 (s, 1 H), 14.56 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 1.59 (m, 4 H), 2.33 (t, $J=5.70$ Hz, 2 H), 2.41 (m, 2 H), 5.14 (s, 2 H), 7.11 (d, $J=8.09$ Hz, 1 H), 7.18 (d, $J=8.09$ Hz, 1 H), 7.25 (m, 3 H), 7.41 (d, $J=7.72$ Hz, 1 H), 7.50 (td, $J=7.72, 1.47$ Hz, 1 H), 7.62 (dd, $J=7.72, 1.47$ Hz, 1 H), 17.13 (s, 1 H).

Example 114

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(4-pyridinylmethyl)thieno[2,3-b]pyridin-6(7H)-one

Example 114A2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared by the method of Fabis, and coworkers in *Tetrahedron* **1998** 54 10789-10800. MS (DCI/NH₃) m/z 187 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 7.17 (d, $J=16.8$ Hz, 1 H) 7.21 (d, $J=16.8$ Hz 1 H) 12.56 (brs, 1 H).

Example 114B1-(pyridin-4-ylmethyl)-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 114A for the product of Example 1A and substituting 4-bromomethyl pyridine hydrobromide for n-butyl bromide (0.22 g, 95%).

Example 114C

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(4-pyridinylmethyl)thieno[2,3-b]pyridin-6(7H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 114B for the product of Example 1B (0.047 g, 13%). MS (DCI/NH₃) m/z 439 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.62 (s, 2 H) 7.48 (m, 2 H) 7.55 (t, $J=7.54$ Hz, 1 H) 7.62 (d, $J=7.72$ Hz, 1 H) 7.68 (d, $J=6.25$ Hz, 1 H) 7.76 (ddd, $J=8.55, 7.26, 1.47$ Hz, 1 H) 7.93 (d, $J=8.09$ Hz, 1 H) 8.71 (d, $J=6.62$ Hz, 1 H) 13.87 (s, 1 H).

Example 115

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(3-pyridinylmethyl)thieno[3,2-b]pyridin-5(4H)-one

Example 115A

1-(pyridin-3-ylmethyl)-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 3-bromomethyl pyridine hydrobromide for n-butyl bromide (0.28 g, 90%). MS (DCI/NH₃) m/z 261 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.24 (s, 2 H) 7.34 (d, J=5.52 Hz, 1 H) 7.38 (m, 1 H) 7.81 (dt, J=8.00, 1.88 Hz, 1 H) 8.30 (d, J=5.15 Hz, 1 H) 8.51 (dd, J=4.78, 1.47 Hz, 1 H) 8.67 (d, J=1.84 Hz, 1 H).

Example 115B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(3-pyridinylmethyl)thieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 115A for the product of Example 1B (0.237 g, 50%). MS (DCI/NH₃) m/z 439 (M+H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 5.49 (s, 2 H) 7.34 (dd, J=7.91, 4.60 Hz, 1 H) 7.45 (m, 3 H) 7.68 (m, 2 H) 7.83 (d, J=8.09 Hz, 1 H) 8.16 (s, 1 H) 8.47 (d, J=3.68 Hz, 1 H) 8.62 (s, 1 H) 14.83 (brs, 1 H).

Example 116

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxythieno[2,3-b]pyridin-6(7H)-one

Example 116A

1-benzyl-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 110B substituting the product of Example 114A for the product of Example 110A (0.26g, 100%).

Example 116B

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxythieno[2,3-b]pyridin-6(7H)-one

The title compound was prepared according to the procedure of Example 1D

substituting the product of Example 116A for the product of Example 1B (0.144 g, 38%). MS (ESI-) m/z 436 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) m/z 436 (M-H)⁻; δ ¹H NMR (300 MHz, DMSO-d₆) δ 5.14 (s, 2 H) 6.90 (d, $J=5.52$ Hz, 1 H) 7.20 (m, 2 H) 7.30 (m, 6 H) 7.54 (m, 1 H) 7.65 (dd, $J=7.72, 1.47$ Hz, 1 H) 16.25 (s, 1 H).

Example 117

4-(cyclopropylmethyl)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

Example 117A

1-(cyclopropylmethyl)-2H-thieno[3,2-*d*][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting bromomethyl cyclopropane for n-butyl bromide (0.23g, 87%). MS (DCI/NH₃) m/z 241 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 0.47 (m, 4 H) 1.21 (m, 1 H) 3.89 (d, $J=6.99$ Hz, 2 H) 7.45 (d, $J=5.15$ Hz, 1 H) 8.35 (d, $J=5.15$ Hz, 1 H).

Example 117B

4-(cyclopropylmethyl)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 117A for the product of Example 1B (0.252 g, 60%). MS (ESI-) m/z 400 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.41 (m, 4 H) 1.20 (m, 1 H) 3.92 (d, $J=6.99$ Hz, 2 H) 7.19 (m, 2 H) 7.26 (t, $J=7.54$ Hz, 1 H) 7.53 (m, 1 H) 7.64 (d, $J=6.62$ Hz, 1 H) 7.79 (d, $J=5.52$ Hz, 1 H) 15.97 (s, 1 H).

Example 118

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(3-methylbutyl)thieno[2,3-b]pyridin-6(7H)-one

Example 118A

1-(3-methylbutyl)-2H-thieno[2,3-*d*][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 114A for the product of Example 1A and substituting isobutyl bromide for n-butyl bromide (0.074 g, 35%).

Example 118B

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(3-methylbutyl)thieno[2,3-b]pyridin-6(7H)-one

5 The title compound was prepared according to the procedure of Example 1D substituting the product of Example 118A for the product of Example 1B (0.063 g, 49%). MS (ESI-) m/z 416 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.96 (s, 3 H) 0.98 (s, 3 H) 1.53 (m, 2 H) 1.66 (m, 1 H) 3.87 (m, 2 H) 6.95 (d, J=5.52 Hz, 1 H) 7.19 (m, 2 H) 7.25 (m, 1 H) 7.52 (ddd, J=8.27, 7.17, 1.47 Hz, 1 H) 7.64 (dd, J=7.72, 1.47 Hz, 1 H) 16.30 (s, 1 H).

Example 119

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-2-phenylthieno[3,2-b]pyridin-5(4H)-one

Example 119A

6-phenyl-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

Methyl-3-amino-5-phenylthiophene-2-carboxylate (0.25 g, 1.07 mmol) in water (6 mL) was reacted with potassium hydroxide (0.12 g, 2.14 mmol) at 90 °C for 24 hours. The reaction was cooled to 0 °C and phosgene (1.9M in toluene, 0.70 mL, 1.40 mmol) was added dropwise. After stirring at room temperature for 1 hour, the resulting solid was collected by filtration, washed with excess water and dried to give the title compound as a tan solid (0.175 g, 65%).

Example 119B

1-benzyl-6-phenyl-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 119A for the product of Example 1A (0.19g, 80%). MS (DCI/NH₃) m/z 353 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.26 (s, 2 H) 7.43 (m, 8 H) 7.82 (m, 3 H).

Example 119C

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-2-phenylthieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 119B for the product of Example 1B (0.062 g, 22%). MS (ESI-) m/z 512 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 5.34 (s, 2 H) 7.24 (m, 2 H)

7.33 (m, 5 H) 7.43 (m, 4 H) 7.56 (t, $J=7.35$ Hz, 1 H) 7.71 (m, 3 H) 15.82 (m, 1 H).

Example 120

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-3-methylthieno[3,2-b]pyridin-5(4H)-one

Example 120A

7-methyl-2H-thieno[3,2- d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 119A substituting methyl-3-amino-4-methylthiophene-2-carboxylate for methyl-3-amino-5-phenylthiophene-2-carboxylate.

Example 120B

1-benzyl-7-methyl-2H-thieno[3,2- d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 110B substituting the product of Example 120A for the product of Example 110A (0.22g, 73%). MS (DCI/ NH_3) m/z 291 ($\text{M}+\text{NH}_4$)⁺

Example 120C

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-3-methylthieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 120B for the product of Example 1B (0.110 g, 30%). MS (ESI-) m/z 450 ($\text{M}-\text{H}$)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d_6) δ 2.21 (s, 3 H) 5.47 (s, 2 H) 7.05 (m, 1 H) 7.25 (m, 6 H) 7.37 (d, $J=0.74$ Hz, 1 H) 7.54 (ddd, $J=8.27, 7.17, 1.47$ Hz, 1 H) 7.64 (dd, $J=7.91, 1.29$ Hz, 1 H) 15.92 (s, 1 H).

Example 121

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6,7,8-tetrahydro-2(1H)-quinolinone

Example 121A

1-benzyl-5,6,7,8-tetrahydro-2H-3,1-benzoxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 113A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.620 g, 67%). MS (ESI-) m/z 256 ($\text{M}-\text{H}$)⁻.

Example 121B1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6,7,8-tetrahydro-2(1H)-quinolinone

5 The title compound was prepared according to the procedure of Example 1D substituting the product of Example 121A for the product of Example 1B (0.039 g, 37%). MS (ESI-) m/z 434 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D: ¹H NMR (300 MHz, DMSO-d₆) δ 1.54 (m, 4 H), 2.33 (t, J=5.88 Hz, 2 H), 2.42 (m, 2 H), 5.15 (s, 2 H), 7.10 (d, J=6.99 Hz, 2 H), 7.20 (m, 3 H), 7.30 (t, J=7.35 Hz, 2 H), 7.50 (td, J=7.72, 1.47 Hz, 1 H), 7.61 (dd, J=7.72, 1.10 Hz, 1 H), 17.20 (s, 1 H).

Example 1221-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2(1H)-pyridinoneExample 122A2H-1,3-oxazine-2,6(3H)-dione

15 The title compound was prepared by the method described by Warren, and coworkers in *Journal of Organic Chemistry* **1975** 40(6) 743-746. MS (DCI/NH₃) m/z 131 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 5.61 (d, J=7.72 Hz, 1 H) 7.65 (d, J=7.35 Hz, 1 H) 11.55 (s, 1 H).

Example 122B3-benzyl-2H-1,3-oxazine-2,6(3H)-dione

25 The title compound was prepared according to the procedure of Example 110B substituting the product of Example 122A for the product of Example 110A (0.156 g, 25%). MS (DCI/NH₃) m/z 221 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 4.89 (s, 2 H) 5.78 (d, J=7.72 Hz, 1 H) 7.37 (m, 5 H) 7.97 (d, J=8.09 Hz, 1 H).

Example 122C1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2(1H)-pyridinone

30 The title compound was prepared according to the procedure of Example 1D substituting the product of Example 122B for the product of Example 1B (0.13 g, 5%). MS (ESI-) m/z 380 (M-H)⁻; ¹H NMR (300 MHz, DMSO-d₆) δ 4.89 (s, 2 H) 5.53 (d, J=7.35 Hz, 1 H) 7.11 (d, J=7.72 Hz, 1 H) 7.28 (m, 6 H) 7.39 (d, J=7.72 Hz, 1 H) 7.50 (m, 1 H) 7.61 (dd, J=7.72, 1.10 Hz, 1 H) 16.83 (s, 1 H).

Example 123

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-2(1H)-pyridinone

Example 123A

4,5-dimethyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared by the method described by Washburne, et. al. *Tetrahedron Letters* **1976** 17(4) 243-246. MS (DCI/NH₃) m/z 204 (M+H)⁺

Example 123B

3-benzyl-4,5-dimethyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 123A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.109 g, 27%). MS (DCI/NH₃) m/z 249 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 1.86 (s, 3 H) 2.14 (s, 3 H) 5.09 (s, 2 H) 7.32 (m, 5 H).

Example 123C

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 123B for the product of Example 1B (0.070 g, 36%). MS (ESI-) m/z 408 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 1.88 (s, 3 H) 2.10 (s, 3 H) 5.20 (s, 2 H) 7.13 (m, 2 H) 7.21 (m, 2 H) 7.31 (m, J=7.17, 7.17 Hz, 3 H) 7.50 (m, 1 H) 7.62 (dd, J=7.91, 1.29 Hz, 1 H) 17.28 (s, 1 H).

Example 124

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-methylthieno[2,3-b]pyridin-6(7H)-one

Example 124A

5-methyl-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Fabis, and co-workers as described in *Tetrahedron*, 1998, 54, 10789-10800. MS (ESI-) m/z 182 (M-H)⁻.

Example 124B

1-benzyl-5-methyl-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 124A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.075 g, 50%). MS (DCI/NH₃) m/z 291 (M+NH₄)⁺.

5

Example 124C

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-methylthieno[2,3-b]pyridin-6(7H)-one

10

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 124B for the product of Example 1B (0.025 g, 23%). MS (ESI-) m/z 450 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 2.46 (s, 3 H), 5.12 (s, 2 H), 6.47 (d, J=1.10 Hz, 1 H), 7.28 (m, 7 H), 7.52 (td, J=7.72, 1.47 Hz, 1 H), 7.64 (dd, J=7.72, 1.47 Hz, 1 H), 16.31 (s, 1 H).

15

Example 125

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(3-methylbutyl)thieno[3,2-b]pyridin-5(4H)-one

20

Example 125A

1-(3-methylbutyl)-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 1-bromo-3-methyl butane for n-butyl bromide (0.246 g, 68%).

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Example 125B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(3-methylbutyl)thieno[3,2-b]pyridin-5(4H)-one

30

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 125A for the product of Example 1B (0.223 g, 52%). MS (ESI-) m/z 416 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.96 (d, J=6.90 Hz, 6 H) 1.45 (m, 2 H) 1.67 (m, 1 H) 3.99 (m, 2 H) 7.09 (d, J=5.52 Hz, 1 H) 7.19 (d, J=7.72 Hz, 1 H) 7.26 (m, 1 H) 7.53 (ddd, J=8.55, 7.26, 1.47 Hz, 1 H) 7.64 (dd, J=7.72, 1.47 Hz, 1 H) 7.80 (d, J=5.52 Hz, 1 H) 15.95 (s, 1 H).

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Example 126

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-(2-ethylbutyl)-7-hydroxythieno[3,2-

bipyridin-5(4H)-oneExample 126A1-(2-ethylbutyl)-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

5 The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 1-bromo-2-ethyl butane for n-butyl bromide (0.116 g, 31%). MS (DCI/NH₃) m/z 271 (M+NH₄)⁺.

Example 126B6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-(2-ethylbutyl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 126A for the product of Example 1B (0.052 g, 26%).

15 MS (ESI-) m/z 430 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.87 (t, J=7.35 Hz, 6 H) 1.29 (m, 4 H) 1.73 (m, J=13.24, 6.99 Hz, 1 H) 3.91 (d, J=7.35 Hz, 2 H) 7.08 (d, J=5.52 Hz, 1 H) 7.18 (d, J=8.09 Hz, 1 H) 7.25 (m, J=7.54, 7.54 Hz, 1 H) 7.53 (ddd, J=8.55, 7.26, 1.47 Hz, 1 H) 7.64 (dd, J=7.72, 1.47 Hz, 1 H) 7.78 (d, J=5.15 Hz, 1 H) 15.99 (s, 1 H).

Example 1271-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-5-phenyl-2(1H)-pyridinoneExample 127A4-methyl-5-phenyl-2H-1,3-oxazine-2,6(3H)-dione

25 Ethyl 2-phenylacetoacetate (1.0 g, 4.85 mmol) and urethane (0.43 g, 4.85 mmol) were heated, neat, with Phosphorous oxychloride (3 mL) at 90 °C for 3 hours. The excess reagents were removed under vacuum and the resulting residue was triturated with benzene and
30 filtered. This solid was triturated with diethyl ether, filtered, and dried to yield 0.818 g (83%). MS (DCI/NH₃) m/z 204 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 1.98 (s, 3 H) 7.28 (m, 2 H) 7.39 (m, 3 H) 11.65 (s, 1 H).

Example 127B3-benzyl-4-methyl-5-phenyl-2H-1,3-oxazine-2,6(3H)-dione

35 The title compound was prepared according to the procedure of Example 1B

substituting the product of Example 127A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.257 g, 71%). MS (DCI/NH₃) m/z 311 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 2.03 (s, 3 H) 5.16 (s, 2 H) 7.34 (m, 10 H).

5

Example 127C1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-5-phenyl-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 127B for the product of Example 1B (0.022 g, 5%). MS (ESI-) m/z 470 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 1.92 (s, 3 H) 5.24 (s, 2 H) 7.19 (m, 10 H) 7.33 (m, 2 H) 7.46 (ddd, J=8.27, 7.17, 1.47 Hz, 1 H) 7.61 (dd, J=7.91, 1.29 Hz, 1 H) 16.97 (s, 1 H).

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Example 1283-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-1-(3-methylbutyl)-2(1H)-pyridinoneExample 128A4,5-dimethyl-3-(3-methylbutyl)-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 123A for the product of Example 1A and substituting 1-bromo-3-methyl butane for n-butyl bromide (0.224 g, 60%). MS (DCI/NH₃) m/z 255 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (d, J=6.62 Hz, 6 H) 1.46 (m, 2 H) 1.59 (dt, J=13.14, 6.48 Hz, 1 H) 1.85 (s, 3 H) 2.26 (s, 3 H) 3.77 (m, 2 H).

20

25

Example 128B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-1-(3-methylbutyl)-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 128A for the product of Example 1B (0.132 g, 32%). MS (ESI-) m/z 388 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.94 (d, J=2.5 Hz, 6H) 1.87 (s, 3H) 2.24 (s, 3H) 3.84 (m, 2H) 7.16 (m, 1H) 7.21 (m, 1H) 7.49 (m, 1H) 7.61 (m, 1H) 17.41 (s, 1H).

30

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Example 129

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-5,6-dimethyl-
2(1H)-pyridinone

Example 129A

3-(2-ethylbutyl)-4,5-dimethyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 123A for the product of Example 1A and substituting 1-bromo-2-ethyl-butane for n-butyl bromide (0.181 g, 45%). ¹H NMR (300 MHz, DMSO- d₆) δ 0.85 (t, J=7.35 Hz, 6 H) 1.29 (m, 4 H) 1.65 (m, 1 H) 1.86 (s, 3 H) 2.25 (s, 3 H) 3.73 (d, J=7.35 Hz, 2 H).

Example 129B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-5,6-dimethyl-
2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 129A for the product of Example 1B (0.027 g, 9%). MS (ESI-) m/z 402 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.85 (t, J=7.35 Hz, 6 H) 1.25 (m, 4 H) 1.62 (m, 1 H) 1.88 (s, 3 H) 2.22 (s, 3 H) 3.82 (m, 2 H) 7.14 (d, J=7.72 Hz, 1 H) 7.21 (m, 1 H) 7.48 (ddd, J=8.46, 7.17, 1.65 Hz, 1 H) 7.60 (dd, J=7.91, 1.29 Hz, 1 H) 17.42 (s, 1 H).

Example 130

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-phenyl-2(1H)-
pyridinone

Example 130A

4-phenyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of Example 127A, substituting ethyl benzoylacetate for ethyl 2-phenylacetoacetate to yield the desired product (0.99 g, 47%). MS (DCI/NH₃) m/z 188 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 6.03 (s, 1 H) 7.56 (m, 3 H) 7.79 (m, 2 H) 11.80 (s, 1 H).

Example 130B

3-benzyl-4-phenyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 130A for the product of Example 1A and benzyl bromide

for n-butyl bromide (0.223 g, 78%).

Example 130C

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-phenyl-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 130B for the product of Example 1B (0.021 g, 6%). MS (ESI⁻) m/z 456 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 4.89 (s, 2 H) 5.44 (s, 1 H) 6.87 (d, J=6.99 Hz, 1 H) 7.20 (m, 9 H) 7.35 (m, 2 H) 7.52 (ddd, J=8.55, 7.26, 1.47 Hz, 1 H) 7.63 (dd, J=7.72, 1.47 Hz, 1 H) 16.78 (s, 1 H).

Example 131

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(3-methyl-2-butenyl)thieno[2,3-b]pyridin-6(7H)-one

Example 131A

1-(3-methylbut-2-enyl)-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 114A for the product of Example 1A and substituting 1-bromo-3-methyl-but-2-ene for n-butyl bromide (0.23 g, 82%). MS (DCI/NH₃) m/z 255 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 1.72 (d, J=1.10 Hz, 3 H) 1.79 (d, J=0.74 Hz, 3 H) 4.50 (d, J=6.62 Hz, 2 H) 5.23 (m, 1 H) 7.28 (d, J=1.10 Hz, 2 H).

Example 131B

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-7-(3-methyl-2-butenyl)thieno[2,3-b]pyridin-6(7H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 131A for the product of Example 1B (0.178 g, 44%). MS (ESI⁻) m/z 414 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 1.69 (s, 3 H) 1.82 (s, 3 H) 4.51 (d, J=6.62 Hz, 2 H) 5.13 (m, 1 H) 6.94 (d, J=5.52 Hz, 1 H) 7.20 (m, 2 H) 7.25 (m, 1 H) 7.53 (ddd, J=8.27, 7.17, 1.47 Hz, 1 H) 7.64 (dd, J=7.72, 1.47 Hz, 1 H) 16.30 (s, 1 H).

Example 132

1,5-dibenzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-2(1H)-pyridinone

Example 132A5-benzyl-4-methyl-2H-1,3-oxazine-2,6(3H)-dione

The title compound was prepared according to the procedure of in Example 127A,
5 substituting ethyl 2-benzyl-3-oxo-butyric acid ethyl ester for ethyl 2-phenylacetoacetate to
yield the desired product. MS (DCI/NH₃) m/z 218 (M+H)⁺

Example 132B3,5-dibenzyl-4-methyl-2H-1,3-oxazine-2,6(3H)-dione

10 The title compound was prepared according to the procedure of Example 1B
substituting the product of Example 132A for the product of Example 1A and benzyl bromide
for n-butyl bromide (0.215 g, 76%).

Example 132C

15 1,5-dibenzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-2(1H)-
pyridinone

The title compound was prepared according to the procedure of Example 1D
substituting the product of Example 132B for the product of Example 1B (0.051 g, 15%).
MS (ESI-) m/z 484 (M-H)⁻. The sodium salt of the title compound was prepared according to
20 the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 2.05 (s, 3 H) 3.84 (s, 2 H)
5.21 (s, 2 H) 7.21 (m, 12 H) 7.49 (m, 1 H) 7.62 (dd, J=7.91, 1.29 Hz, 1 H) 17.10 (s, 1 H).

Example 133

25 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-6-methyl-5-
phenyl-2(1H)-pyridinone

Example 133A3-(2-ethylbutyl)-4-methyl-5-phenyl-2H-1,3-oxazine-2,6(3H)-dione

30 The title compound was prepared according to the procedure of Example 1B
substituting the product of Example 127A for the product of Example 1A and substituting 1-
bromo-2-ethyl butane for n-butyl bromide (0.145 g, 41%). MS (DCI/NH₃) m/z 288 (M+H)⁺

Example 133B

35 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-6-methyl-5-
phenyl-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 133A for the product of Example 1B (0.019 g, 8%). MS (ESI-) m/z 464 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.88 (t, $J=7.35$ Hz, 6 H) 1.30 (m, 4 H) 1.71 (m, 1 H) 2.03 (s, 3 H) 3.83 (m, 2 H) 7.10 (m, 3 H) 7.22 (m, 2 H) 7.34 (t, $J=7.17$ Hz, 2 H) 7.45 (ddd, $J=8.27, 7.17, 1.47$ Hz, 1 H) 7.60 (dd, $J=7.91, 1.29$ Hz, 1 H) 17.10 (s, 1 H).

Example 134

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-pentylthieno[3,2-b]pyridin-5(4H)-one

Example 134A

1-pentyl-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting n-pentyl bromide for n-butyl bromide (0.205 g, 72%).

Example 134B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-pentylthieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 134A for the product of Example 1B (0.189 g, 53%). MS (ESI-) m/z 416 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.88 (m, 3 H) 1.33 (m, 4 H) 1.57 (m, 2 H) 3.97 (m, 2 H) 7.14 (d, $J=5.52$ Hz, 1 H) 7.18 (d, $J=8.09$ Hz, 1 H) 7.25 (m, 1 H) 7.53 (m, 1 H) 7.64 (dd, $J=7.91, 1.29$ Hz, 1 H) 7.79 (d, $J=5.52$ Hz, 1 H) 15.96 (s, 1 H).

Example 135

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-methyl-7-(3-methylbutyl)thieno[2,3-b]pyridin-6(7H)-one

Example 135A

5-methyl-2H-thieno[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared from 2-amino-4-methyl-thiophene-3-carboxylic acid ethyl ester according to the procedure of Fabis, and co-workers as described in *Tetrahedron*, 1998, 54, 10789-10800 MS (ESI) m/z 182 (M-H)⁻; ¹H NMR (300 MHz, DMSO-

D₆) δ ppm 2.30 (d, $J=1.47$ Hz, 3 H), 6.78 (s, 1 H), 12.51 (s, 1 H).

Example 135B

5-methyl-1-(3-methylbutyl)-2H-thieno[2,3-*d*][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 135A for the product of Example 1A and substituting isopentyl bromide for n-butyl bromide (0.048 g, 30%). MS (DCI/NH₃) m/z 254 (M+H)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.94 (d, $J=6.25$ Hz, 6 H), 1.61 (m, 3 H), 2.33 (d, $J=1.10$ Hz, 3 H), 3.83 (m, 2 H), 6.92 (d, $J=1.10$ Hz, 1 H).

Example 135C

5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-methyl-7-(3-methylbutyl)thieno[2,3-*b*]pyridin-6(7H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 135B for the product of Example 1B (0.043 g, 52%). MS (DCI/NH₃) m/z 430 (M+H)⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.98 (d, $J=6.25$ Hz, 6 H), 1.67 (m, 3 H), 2.50 (s, 3 H), 4.13 (m, 2 H), 7.08 (s, 1 H), 7.55 (t, $J=7.54$ Hz, 1 H), 7.68 (d, $J=8.46$ Hz, 1 H), 7.77 (t, $J=7.17$ Hz, 1 H), 7.92 (d, $J=7.35$ Hz, 1 H), 14.30 (s, 1 H), 15.22 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.97 (d, $J=6.62$ Hz, 6 H), 1.56 (m, 3 H), 3.89 (m, 2 H), 7.53 (m, 5 H), 16.37 (brs, 1 H).

Example 136

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(4-methylpentyl)thieno[3,2-*b*]pyridin-5(4H)-one

Example 136A

1-(4-methylpentyl)-2H-thieno[3,2-*d*][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 1-bromo-4-methyl-pentane for n-butyl bromide (0.110 g, 61%).

Example 136B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(4-methylpentyl)thieno[3,2-*b*]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D

substituting the product of Example 136A for the product of Example 1B (0.064 g, 34%). MS (ESI-) m/z 430 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.86 (s, 3 H) 0.88 (s, 3 H) 1.24 (m, $J=15.81$, 6.99 Hz, 2 H) 1.56 (m, 3 H) 3.96 (d, $J=6.99$ Hz, 2 H) 7.16 (m, 1 H) 7.26 (t, $J=7.35$ Hz, 1 H) 7.53 (t, $J=7.72$ Hz, 1 H) 7.64 (d, $J=7.72$ Hz, 1 H) 7.80 (d, $J=5.15$ Hz, 1 H) 15.96 (s, 1 H).

Example 137

4-(3-butenyl)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

Example 137A

1-but-3-enyl-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 4-bromo-but-1-ene for n-butyl bromide (0.09 g, 56%).

Example 137B

4-(3-butenyl)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 137A for the product of Example 1B (0.062 g, 38%). MS (ESI-) m/z 399.9 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz; DMSO- d₆) δ 2.34 (q, $J=7.23$ Hz, 2 H) 4.04 (m, 2 H) 5.05 (m, 2 H) 5.87 (m, 1 H) 7.18 (m, 2 H) 7.25 (t, $J=7.17$ Hz, 1 H) 7.53 (m, 1 H) 7.64 (d, $J=6.62$ Hz, 1 H) 7.79 (d, $J=5.52$ Hz, 1 H) 15.93 (s, 1 H).

Example 138

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one

Example 138A

ethyl 5-(benzylamino)-1-phenyl-1H-pyrazole-4-carboxylate

The title compound was prepared according to the procedure of Example 1B substituting ethyl 5-amino-1-phenyl-4-pyrazole-carboxylate for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.990g, 83%). MS (ESI-) m/z 320(M-

H).

Example 138B

ethyl 5-[benzyl(3-ethoxy-3-oxopropanoyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate

The title compound was prepared (51% yield) from the product of Example 138A and ethyl malonyl chloride according to the procedure of Rowley, and co-workers as described in *J. Med. Chem.*, 1993, 36, 3386-3396. MS (ESI-) m/z 434 (M-H)⁺.

Example 138C

methyl 7-benzyl-4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

The title compound was prepared from the product of Example 138B and sodium methoxide according to the procedure of Rowley, and co-workers as described in *J. Med. Chem.*, 1993, 36, 3386-3396. MS (ESI-) m/z 374 (M-H)⁺.

Example 138D

N-[2-(aminosulfonyl)phenyl]-7-benzyl-4-hydroxy-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

The title compound was prepared according to the procedure of Example 84C substituting the product of Example 138C for the product of Example 84B and 2-aminobenzenesulfonamide for 2-amino-5-bromobenzenesulfonamide (0.014 g, 61%). MS (ESI+) m/z 516 (M+H)⁺.

Example 138E

7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-phenyl-1,7-dihydro-6H-pyrazolo[3,4-b]pyridin-6-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 138D for the product of Example 84C (0.061 g, 84%). MS (ESI-) m/z 496 (M-H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 4.92 (s, 2 H), 6.53 (m, 2 H), 7.21 (m, 9 H), 7.43 (t, J=7.35 Hz, 1 H), 7.54 (td, J=7.81, 1.65 Hz, 1 H), 7.64 (dd, J=7.91, 1.29 Hz, 1 H), 7.88 (s, 1 H), 16.05 (s, 1 H).

Example 139

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-2,7-dihydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

Example 139Amethyl 4-(benzylamino)-2-(methylthio)-1,3-thiazole-5-carboxylate

The title compound was prepared according to the procedure of Example 1B substituting 4-amino-2-methylthio-5-thiazolecarboxylic acid methyl ester for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.411 g, 57%). MS (ESI+) m/z 295 (M+H)⁺.

Example 139Bmethyl 4-[benzyl(3-ethoxy-3-oxopropanoyl)amino]-2-(methylthio)-1,3-thiazole-5-carboxylate

The title compound was prepared according to the procedure of Example 138B substituting the product of Example 139A for the product of Example 138A (0.147 g, 30%). MS (ESI+) m/z 409 (M+H)⁺.

Example 139Cethyl 4-benzyl-7-hydroxy-2-(methylthio)-5-oxo-4,5-dihydro[1,3]thiazolo[4,5-b]pyridine-6-carboxylate

The title compound was prepared according to the procedure of Example 138C substituting the product of Example 139B for the product of Example 138B (0.111g, 82%). MS (ESI-) m/z 375 (M-H)⁻.

Example 139DN-[2-(aminosulfonyl)phenyl]-4-benzyl-7-hydroxy-2-(methylthio)-5-oxo-4,5-dihydro[1,3]thiazolo[4,5-b]pyridine-6-carboxamide

The title compound was prepared according to the procedure of Example 84C substituting the product of Example 139C for the product of Example 84B and 2-aminobenzenesulfonamide for 2-amino-5-bromobenzenesulfonamide (0.114 g, 75%). MS (ESI-) m/z 501 (M-H)⁻.

Example 139E4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-2,7-dihydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 139D for the product of Example 84C (0.108 g, 60%). MS (ESI-) m/z 453 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d₆) δ 5.37 (s, 2 H), 7.29 (m, 5 H),

7.44 (t, $J=7.72$ Hz, 1 H), 7.50 (d, $J=7.72$ Hz, 1 H), 7.67 (td, $J=7.72$, 1.47 Hz, 1 H), 7.82 (d, $J=7.72$ Hz, 1 H), 14.01 (s, 1 H), 14.32 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 5.13 (s, 2 H), 7.04 (d, $J=8.09$ Hz, 1 H), 7.20 (m, 6 H), 7.45 (t, $J=7.35$ Hz, 1 H), 7.56 (d, $J=7.72$ Hz, 1 H), 17.25 (s, 1 H).

Example 140

4-[(2-chloro-1,3-thiazol-5-yl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

Example 140A

1-[(2-chloro-1,3-thiazol-5-yl)methyl]-2H-thieno[3,2- d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 104A for the product of Example 1A and substituting 2-chloro-5-bromomethylthiazole for *n*-butyl bromide (0.341 g, 75%). MS (DCI/ NH_3) m/z 301 ($\text{M}+\text{H}$) $^+$. ^1H NMR (300 MHz, DMSO- d_6) δ 5.35 (s, 2 H), 7.60 (d, $J=5.15$ Hz, 1 H), 7.89 (s, 1 H), 8.38 (d, $J=5.52$ Hz, 1 H),

Example 140B

4-[(2-chloro-1,3-thiazol-5-yl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 140A for the product of Example 1B (0.134 g, 40%). MS (ESI-) m/z 477 ($\text{M}-\text{H}$) $^-$. ^1H NMR (300 MHz, DMSO- d_6) δ 5.64 (s, 2 H), 7.55 (t, $J=7.17$ Hz, 1 H), 7.67 (d, $J=7.72$ Hz, 1 H), 7.78 (t, $J=7.17$ Hz, 1 H), 7.86 (d, $J=5.52$ Hz, 1 H), 7.93 (d, $J=7.72$ Hz, 1 H), 7.95 (s, 1 H), 8.43 (d, $J=5.52$ Hz, 1 H), 14.10 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

Example 141

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(5-methyl-3-pyridinyl)methyl]thieno[3,2-b]pyridin-5(4H)-one

Example 141A

1-[(5-methylpyridin-3-yl)methyl]-2H-thieno[3,2- d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 3-

methyl-5-chloromethylpyridine for n-butyl bromide (0.255g, 38%). MS (DCI/NH₃) m/z 275 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d₆) δ 2.27 (s, 3 H), 5.21 (s, 2 H), 7.31 (d, J=5.52 Hz, 1 H), 7.63 (s, 1 H), 8.29 (d, J=5.15 Hz, 1 H), 8.34 (d, J=1.47 Hz, 1 H), 8.47 (d, J=1.84 Hz, 1 H).

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Example 141B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(5-methyl-3-pyridinyl)methyl]thieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 141A for the product of Example 1B (0.175 g, 43%). MS (ESI-) m/z 451 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d₆) δ 2.25 (s, 3 H), 5.54 (s, 2 H), 7.53 (m, 3 H), 7.64 (d, J=7.72 Hz, 1 H), 7.75 (td, J=7.72, 1.47 Hz, 1 H), 7.92 (d, J=7.35 Hz, 1 H), 8.34 (d, J=5.15 Hz, 1 H), 8.34 (s, 1 H), 8.45 (d, J=1.47 Hz, 1 H), 14.30 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

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Example 142

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methyl-1,3-thiazol-5-yl)methyl]thieno[3,2-b]pyridin-5(4H)-one

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Example 142A

1-[(2-methyl-1,3-thiazol-5-yl)methyl]-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 2-methyl-5-chloromethylthiazole for n-butyl bromide (0.308g, 55%). MS (DCI/NH₃) m/z 281 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d₆) δ 2.59 (s, 3 H), 5.34 (s, 2 H), 7.58 (d, J=5.52 Hz, 1 H), 7.81 (s, 1 H), 8.37 (d, J=5.52 Hz, 1 H).

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Example 142B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methyl-1,3-thiazol-5-yl)methyl]thieno[3,2-b]pyridin-5(4H)-one

30

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 142A for the product of Example 1B (0.151 g, 40%). MS (DCI/NH₃) m/z 459 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d₆) δ 2.56 (s, 3 H), 5.65 (s, 2 H), 7.56 (t, J=7.17 Hz, 1 H), 7.68 (d, J=7.72 Hz, 1 H), 7.79 (m, 3 H), 7.93 (d, J=7.72 Hz, 1 H), 8.42 (d, J=5.52 Hz, 1 H), 14.18 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

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Example 143

4-[(5-chloro-2-thienyl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

Example 143A

1-[(5-chloro-2-thienyl)methyl]-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 2-chloro-5-chloromethylthiophene for n-butyl bromide (0.601g, 100%).

Example 143B

4-[(5-chloro-2-thienyl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 143A for the product of Example 1B (0.115 g, 12%). MS (APCI) m/z 478 (M+H)⁺. ¹H NMR (300 MHz, DMSO-D₆) δ 5.59 (s, 2 H), 6.99 (d, J=3.68 Hz, 1 H), 7.23 (d, J=4.04 Hz, 1 H), 7.56 (t, J=7.72 Hz, 1 H), 7.68 (d, J=7.72 Hz, 1 H), 7.78 (m, 1 H), 7.80 (d, J=5.88 Hz, 1 H), 7.93 (d, J=8.09 Hz, 1 H), 8.41 (d, J=5.52 Hz, 1 H), 14.18 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

Example 144

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methyl-1,3-thiazol-4-yl)methyl]thieno[3,2-b]pyridin-5(4H)-one

Example 144A

1-[(2-methyl-1,3-thiazol-4-yl)methyl]-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 2-methyl-4-chloromethylthiazole hydrochloride for n-butyl bromide (0.200g, 36%).

Example 144B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methyl-1,3-thiazol-4-yl)methyl]thieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 144A for the product of Example 1B (0.127 g, 38%).

MS (ESI+) m/z 459 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d₆) δ 2.60 (s, 3 H), 5.55 (s, 2 H), 7.54 (t, $J=6.99$ Hz, 1 H), 7.54 (d, $J=5.52$ Hz, 1 H), 7.65 (d, $J=7.72$ Hz, 1 H), 7.76 (m, 1 H), 7.92 (d, $J=6.62$ Hz, 1 H), 8.34 (d, $J=5.51$ Hz, 1 H), 14.30 (s, 1 H),

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Example 145

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-2-(methylsulfanyl)[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

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Example 145A

4-benzyl-2-(methylthio)-5H-[1,3]thiazolo[4,5-d][1,3]oxazine-5,7(4H)-dione

The title compound was prepared according to the procedure of Example 3B substituting the product of Example 139A for the product of Example 3A (0.048 g, 92%). MS (DCI/NH₃) m/z 324 (M+NH₄)⁺.

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Example 145B

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-2-(methylsulfanyl)[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 145A for the product of Example 1B (0.037 g, 51%).

20

MS (ESI) m/z 485 (M+H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 2.73 (s, 3 H), 5.31 (s, 2 H), 7.25 (m, 7 H), 7.53 (td, $J=7.72$, 1.47 Hz, 1 H), 7.64 (dd, $J=7.91$, 1.29 Hz, 1 H), 15.52 (s, 1 H).

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Example 146

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-2-(methylsulfonyl)[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

The title compound was prepared as a white solid from the product of Example 145B and 3-chloroperoxybenzoic acid according to the procedure of Leysen, and co-workers described in *J. Heterocyclic Chem.*, 1984, 21, 401-406. MS (ESI) m/z 515 (M-H)⁻; ¹H NMR (300 MHz, DMSO- d₆) δ 3.59 (s, 3 H), 5.51 (s, 2 H), 7.32 (m, 5 H), 7.51 (m, 2 H), 7.69 (m, 1 H), 7.85 (d, $J=7.72$ Hz, 1 H), 13.95 (s, 1 H).

30

Example 147

2-amino-4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

The product of Example 146 (0.011 g, 0.02 mmol) was reacted with ammonia (0.5 M

in dioxane, 1.3 mL, 0.64 mmol) in a pressure tube at 70°C for 17 hours. The reaction was cooled and the resulting precipitate was collected by filtration and dried to give the title compound as a white solid (0.009 g, 100%). MS (ESI) m/z 452 (M-H)⁻; ¹H NMR (300 MHz, DMSO-d₆) δ 5.43 (s, 2 H), 6.91 (s, 1 H), 7.07 (s, 1 H), 7.30 (m, 4 H), 7.52 (dd, $J=24.27$, 8.82 Hz, 2 H), 7.69 (t, $J=7.54$ Hz, 1 H), 7.85 (d, $J=8.82$ Hz, 1 H), 9.03 (br s, 1 H), 14.57 (brs, 1 H).

Example 148

4-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy[1,3]thiazolo[4,5-b]pyridin-5(4H)-one

10

The product of Example 147 (0.0085 g, 0.019 mmol) was reacted with *tert*-butyl nitrite (5 μ L, 0.037 mmol) in DMF (0.3 mL) at 60°C for 1 hour. The reaction was cooled, and the crude mixture was purified by column chromatography with silica gel eluting with hexane and ethyl acetate (1:1) to give the title compound as a yellow solid (0.0045 g, 54%). MS (ESI) m/z 437 (M-H)⁻; ¹H NMR (300 MHz, DMSO-d₆) δ 5.53 (s, 2 H), 7.25 (m, 1 H), 7.31 (m, 4 H), 7.43 (m, 2 H), 7.66 (m, 1 H), 7.80 (d, $J=8.46$ Hz, 1 H), 9.48 (s, 1 H), 14.56 (br s, 1 H).

15

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3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(2-phenylpropyl)-1,8-naphthyridin-2(1H)-one

Example 149A

ethyl 2-[(2-phenylpropyl)amino]nicotinate

25

The title compound was prepared according to the procedure of Example 3A, substituting (\pm)-beta-methylphenethylamine for 2-ethyl-butylamine (0.44 g, 58%). MS (DCI+) m/z 285 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 1.25 (m, 6H), 3.07 (m, 1H), 3.64 (m, 3H), 4.22 (q, $J=6.99$ Hz, 1H), 6.61 (dd, $J=7.72$, 4.78 Hz, 1H), 7.21 (m, 1H), 7.30 (m, 4H), 7.87 (t, $J=5.52$ Hz, 1H), 8.05 (m, 1H), 8.29 (m, 1H).

30

Example 149B

1-(2-phenylpropyl)-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione

35

The title compound was prepared according to the procedure of Example 3B substituting the product of Example 149A for the product of Example 3A (0.44 g, 99%). MS (DCI+) m/z 283 (M+H)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 1.26 (d, $J=6.99$ Hz, 3H), 3.37 (m, 1H), 4.21 (dd, $J=13.24$, 6.25 Hz, 1H), 4.36 (m, 1H), 7.21 (m, 1H), 7.29 (m, 4H), 7.38 (dd, $J=7.72$, 4.78 Hz, 1H), 8.39 (dd, $J=7.72$, 1.84 Hz, 1H), 8.77 (dd, $J=4.78$, 1.84 Hz, 1H).

Example 149C3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(2-phenylpropyl)-1,8-naphthyridin-2(1H)-one

5 The title compound was prepared according to the procedure of Example 1D substituting the product of Example 149B for the product of Example 1B (0.045 g, 62%). MS (ESI-) m/z 459 (M-H)⁻; ¹H NMR (300 MHz, DMSO-D₆) δ 1.23 (d, J=7.35 Hz, 3H), 3.47 (m, 1H), 4.59 (dd, J=12.50, 6.62 Hz, 1H), 4.75 (m, 1H), 7.16 (m, 1H), 7.28 (m, 4H), 7.45 (dd, J=7.91, 4.60 Hz, 1H), 7.56 (t, J=7.54 Hz, 1H), 7.69 (m, 1H), 7.78 (m, 1H), 7.93 (d, J=8.09 Hz, 1H), 8.53 (dd, J=8.09, 1.84 Hz, 1H), 8.80 (dd, J=4.60, 1.65 Hz, 1H), 14.13 (brs, 1H).
10 The sodium salt of the title compound was prepared according to the procedure of Example 1d. ¹H NMR (300 MHz, DMSO-D₆) δ 1.12 (d, J=6.99 Hz, 3H), 3.42 (m, 1H), 4.30 (dd, J=12.50, 5.52 Hz, 1H), 4.67 (dd, J=12.32, 9.74 Hz, 1H), 7.12 (dd, J=7.72, 4.78 Hz, 1H), 7.18 (m, 1H), 7.30 (m, 6H), 7.56 (m, 1H), 7.67 (d, J=7.72 Hz, 1H), 8.36 (dd, J=7.54, 2.02 Hz, 1H),
15 8.50 (dd, J=4.78, 1.84 Hz, 1H), 15.92 (s, 1H).

Example 1508-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxy-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-oneExample 150Aethyl 4-(benzylamino)-2-(methylthio)pyrimidine-5-carboxylate

20 The title compound was prepared according to the procedure of Example 108A substituting benzyl amine for 1-amino-2-ethyl-butane (0.97 g, 92%). MS (DCI/NH₃) m/z 304 (M+H)⁺ ¹H NMR (300 MHz, DMSO- d₆) δ 1.32 (q, J=7.48 Hz, 3 H) 2.41 (s, 3 H) 4.30 (q, J=7.11 Hz, 2 H) 4.73 (d, J=5.88 Hz, 2 H) 7.30 (m, 5 H) 8.58 (s, 1 H) 8.89 (t, J=5.70 Hz, 1 H)

Example 150B4-(benzylamino)-2-(methylthio)pyrimidine-5-carboxylic acid

30 The title compound was prepared according to the procedure of Example 108B substituting the product of Example 150A for the product of Example 108A. (0.185 g, 78%).

Example 150C1-benzyl-7-(methylthio)-2H-pyrimido[4,5-d][1,3]oxazine-2,4(1H)-dione

35 The title compound was prepared according to the procedure of Example 108C substituting the product of Example 150B for the product of Example 108B (0.145 g, 72%).

MS (DCI/NH₃) m/z 302 (M+H)⁺

Example 150D

8-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxy-2-
(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 150C for the product of Example 1B (0.042 g, 18%). MS (ESI⁻) m/z 478 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 2.48 (s, 3 H) 5.41 (s, 2 H) 7.26 (m, 7H) 7.57 (m, 1 H) 7.67 (dd, J=7.54, 0.92 Hz, 1 H) 8.91 (s, 1 H) 15.42 (s, 1 H).

Example 151

8-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxypyrido[2,3-d]pyrimidin-
7(8H)-one

The title compound was prepared according to the procedure of Example 109 substituting the product of Example 151D for the product of Example 108D (0.019 g, 58%). MS (ESI⁻) m/z 432 (M-H)⁻; ¹H NMR (300 MHz, DMSO- d₆) δ 5.44 (s, 2 H) 7.20 (m, 1 H) 7.30 (m, 7 H) 7.57 (m, 1 H) 7.68 (d, J=8.09 Hz, 1 H) 8.94 (s, 1 H) 9.12 (s, 1 H) 15.32 (s, 1 H).

Example 152

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(3-hydroxybutyl)-2(1H)-
quinolinone

A solution of the product of Example 73 (0.12 g, 0.30 mmol) in tetrahydrofuran (6 mL) was treated with 3.0 M methyl magnesium bromide (0.11 mL, 0.33 mmol) at -50 °C, then stirred at room temperature for 1 hour. The solution was diluted with 1N HCl and water then filtered. The resulting solid was triturated with dichloromethane and filtered. The filtrate was concentrated to give the title compound (0.050 g, 40%). MS (DCI/NH₃) m/z 415 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 1.14 (d, J=6.25 Hz, 3 H) 1.75 (dd, J=9.19, 5.52 Hz, 2 H) 3.78 (m, 1 H) 4.57 (m, 2 H) 7.54 (m, 2 H) 7.77 (m, 2 H) 7.94 (d, J=7.35 Hz, 1 H) 8.58 (dd, J=7.91, 2.02 Hz, 1 H) 8.90 (dd, J=4.78, 1.84 Hz, 1 H) 14.12 (s, 1 H).

Example 153

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxythieno[3,4-b]pyridin-
2(1H)-one

Example 153A

4H-thieno[3,4-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to procedure of Example 119A substituting ethyl 3-aminothiophene-5-carboxylate hydrochloride for methyl 3-amino-5-phenylthiophene-carboxylate (0.86 g, 50%). MS (DCI/NH₃) m/z 187 (M+NH₄)⁺; ¹H NMR (300 MHz, DMSO-d₆) δ 6.90 (d, J=9.93 Hz, 1 H) 8.65 (d, J=9.93 Hz, 1 H) 11.57 (brs, 1 H).

Example 153B1-benzyl-4H-thieno[3,4-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 153A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.33g, 91%).

Example 153C1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxythieno[3,4-b]pyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 153B for the product of Example 1B (0.028 g, 5%). MS (ESI-) m/z 436 (M-H)⁻; ¹H NMR (300 MHz, DMSO- d₆) δ 5.13 (s, 2 H) 6.68 (d, J=3.31 Hz, 1 H) 7.21 (m, 2 H) 7.28 (m, 5 H) 7.54 (m, 1 H) 7.64 (m, 1 H) 7.99 (d, J=3.31 Hz, 1 H) 15.83 (s, 1 H).

Example 1544-[(5-bromo-2-thienyl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-oneExample 154A1-[(5-bromothien-2-yl)methyl]-2H-thieno[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 110A for the product of Example 1A and substituting 2-bromo-5-bromomethyl-thiophene for n-butyl bromide (0.25g, 82%).

Example 154B4-[(5-bromo-2-thienyl)methyl]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 154A for the product of Example 1B (0.219 g, 58%). MS (ESI-) m/z 521 (M-H)⁻. The sodium salt of the title compound was prepared according to

the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 5.28 (s, 2 H) 7.02 (d, J=3.68 Hz, 1 H) 7.09 (d, J=3.68 Hz, 1 H) 7.20 (d, J=8.09 Hz, 1 H) 7.27 (m, 1 H) 7.37 (d, J=5.15 Hz, 1 H) 7.54 (ddd, J=8.55, 7.26, 1.47 Hz, 1 H) 7.66 (dd, J=7.72, 1.47 Hz, 1 H) 7.81 (d, J=5.15 Hz, 1 H) 15.80 (s, 1 H).

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Example 155

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-2(1H)-pyridinone

Example 155A

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1-butyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

To a solution of 2-hydroxy-nicotinic acid (0.50 g, 3.59 mmol) and potassium hydroxide (0.40 g, 7.13 mmol) in 4:1 methanol: water (6 mL) at room temperature, was added 1-iodobutane (0.74 mL, 6.42 mmol). This solution was heated at 60 °C for 30 minutes, then cooled to room temperature and diluted with water and 1N HCl. The resulting solid was filtered and dried to give the title compound (0.27 g, 39%). MS (DCI/NH₃) m/z 196 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 0.91 (m, 3 H) 1.30 (m, 2 H) 1.69 (m, 2 H) 4.10 (m, 2 H) 6.73 (m, 1 H) 8.27 (dd, J=6.62, 1.84 Hz, 1 H) 8.38 (dd, J=7.35, 2.21 Hz, 1 H) 14.68 (s, 1 H).

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Example 155B

N-[2-(aminosulfonyl)phenyl]-1-butyl-2-oxo-1,2-dihydropyridine-3-carboxamide

A solution of the product of Example 155A and 2-aminobenzene sulfonamide (0.24 g, 1.39 mmol) in tetrahydrofuran (8 mL) at room temperature and treated with TBTU (O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) and triethylamine (0.58 mL, 4.15 mmol). After 18 hours, the mixture was poured into water, extracted with ethyl acetate, dried over sodium sulfate, filtered and the filtrate evaporated under vacuum and purified by preparative HPLC on a Waters Symmetry C8 column (40mm X 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 12min (15min run time) at a flow rate of 70mL/min to yield the title compound.

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Example 155C

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-2(1H)-pyridinone

The title compound was prepared according to the procedure of Example 84D and purified by preparative HPLC on a Waters Symmetry C8 column (40mm X 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 12min (15min run time) at a flow rate of 70mL/min. MS DCI/NH₃) m/z 332 (M+H)⁺. The sodium salt of the title compound was prepared

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according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.93 (t, J=7.35 Hz, 3 H) 1.34 (td, J=14.89, 7.35 Hz, 2 H) 1.73 (ddd, J=14.89, 7.72, 7.54 Hz, 2 H) 4.13 (m, 2 H) 6.73 (dd, J=7.35, 6.62 Hz, 1 H) 7.50 (m, 1 H) 7.59 (d, J=7.35 Hz, 1 H) 7.71 (m, 1 H) 7.85 (dd, J=7.91, 1.29 Hz, 1 H) 8.30 (dd, J=6.43, 2.02 Hz, 1 H) 8.62 (dd, J=7.54, 2.02 Hz, 1 H) 13.76 (s, 1 H).

Example 156

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridine-2,4-diol

The product of Example 73 (0.12 g, 0.30 mmol) in tetrahydrofuran (6 mL) was reacted with 3.0 M methyl magnesium bromide (0.11 mL, 0.33 mmol) at -50 °C, and then stirred at room temperature for 1 hour. The solution was diluted with 1N HCl and filtered. The resulting solid was triturated with dichloromethane and filtered to yield the product. MS (DCI/NH₃) m/z 343 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 7.46 (dd, J=7.91, 4.60 Hz, 1 H) 7.57 (m, 1 H) 7.64 (d, J=7.72 Hz, 1 H) 7.79 (ddd, J=8.36, 7.26, 1.29 Hz, 1 H) 7.94 (d, J=7.35 Hz, 1 H) 8.49 (dd, J=8.09, 1.84 Hz, 1 H) 8.80 (dd, J=4.60, 1.65 Hz, 1 H) 12.92 (s, 1 H) 14.28 (s, 1 H).

Example 157

1-(benzyloxy)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one

Example 157A

ethyl 2-[(benzyloxy)amino]nicotinate

2-Chloro-nicotinic acid ethyl ester (4.55 g, 24.6 mmol), O-benzylhydroxyamine hydrochloride (7.85 g, 49.2 mmol) and N,N-diisopropylethylamine (6.36 g, 49.2 mmol) in 10 mL 1,4-dioxane were reacted in a sealed tube at 120 °C for 48 hours. The reaction mix was partitioned between ethyl acetate and 5% aqueous sodium bicarbonate. The aqueous layer was re-extracted with ethyl acetate (2 x 50 mL). The organic layers were combined and dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane and ethyl acetate (9:1) to provide the title compound (3.5 g, 53%). MS (DCI) m/z 273 (M+H)⁺.

Example 157B

ethyl 2-[(benzyloxy)(3-ethoxy-3-oxopropanoyl)amino]nicotinate

A solution of the product of Example 157A (1.2 g, 4.4 mmol) and triethylamine (0.49 g, 4.8 mmol) in dichloromethane (25 mL) was treated dropwise with ethyl chloromalonate (0.73 g, 4.8 mmol), stirred for 2 hr and partitioned between ethyl acetate and water and the

layers were separated. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel eluting with hexane and ethyl acetate (3:1) to provide the title compound (1.1 g, 65%). MS (DCI) m/z 387 ($\text{M}+\text{H}$)⁺.

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Example 157C

ethyl 1-(benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

A solution of the product of Example 157B (0.386 g, 1.0 mmol) in ethanol (5 mL) was treated with 21% sodium ethoxide in ethanol (0.324 g, 1.0 mmol), stirred for 30 minutes and partitioned between ethyl acetate and 5% aqueous HCl and the layers were separated. The ethyl acetate layer was washed with brine, dried (Na_2SO_4), and concentrated to provide the title compound (0.28 g, 82%). MS (DCI) m/z 341 ($\text{M}+\text{H}$)⁺.

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Example 157D

N-[2-(aminosulfonyl)phenyl]-1-(benzyloxy)-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide

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The title compound was prepared according to the procedure of Example 84C substituting the product of Example 157C for the product of Example 84B and substituting 2-aminosulfonamide for the product of Example 84A (340 mg, 89% yield). MS (DCI) m/z 467 ($\text{M}+\text{H}$)⁺.

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Example 157E

1-(benzyloxy)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridine-2(1H)-one

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The title compound was prepared according to the procedure of Example 84D substituting the product of Example 157D for the product of Example 84C (0.082 g, 87%). MS (ESI-) m/z 447 ($\text{M}-\text{H}$)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d_6) δ 5.12 (s, 2 H) 7.22 (dd, $J=7.72$, 4.78 Hz, 1 H) 7.30 (m, 2 H) 7.44 (m, 3 H) 7.57 (m, 1 H) 7.70 (m, 3 H) 8.41 (dd, $J=7.72$, 1.84 Hz, 1 H) 8.61 (dd, $J=4.78$, 1.84 Hz, 1 H) 15.70 (s, 1 H).

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Example 158

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-isobutoxy-1,8-naphthyridine-2(1H)-one

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Example 158A

ethyl 2-(isobutoxyamino)nicotinate

The title compound was prepared according to the procedure of Example 157A substituting O-isobutylhydroxylamine hydrochloride for O-benzylhydroxylamine hydrochloride (0.372 g, 34%). MS (DCI) m/z 239 (M+H)⁺.

Example 158B

ethyl 2-[(3-ethoxy-3-oxopropanoyl)(isobutoxy)amino]nicotinate

The title compound was prepared according to the procedure of Example 157B substituting the product of Example 158A for the product of Example 157A (0.230 g, 42%). MS (DCI) m/z 353 ($M+H$)⁺.

Example 158C

ethyl 4-hydroxy-1-isobutoxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate

The title compound was prepared according to the procedure of Example 157C substituting the product of Example 158B for the product of 157B (0.200 g, 99%).

MS (DCI) m/z 307 ($M+H$)⁺.

Example 158D

N-[2-(aminosulfonyl)phenyl]-4-hydroxy-1-isobutoxy-2-oxo-1,2-dihydro-1,8-naphthyridine-
3-carboxamide

The title compound was prepared according to the procedure of Example 84C substituting the product of Example 158C for the product of Example 84B and substituting 2-aminosulfonamide for the product of Example 84A (0.225 g, 86%). MS (DCI) m/z 433 ($M+H$)⁺.

Example 158E

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-isobutoxy-1,8-naphthyridin-
2(1H)-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 158D for the product of Example 84C (0.200 g, 93%). MS (ESI-) m/z 413 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1d. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.05 (d, *J*=6.62 Hz, 6 H) 2.08 (m, 1 H) 3.88 (d, *J*=6.62 Hz, 2 H) 7.18 (dd, *J*=7.72, 4.78 Hz, 1 H) 7.29 (m, 2 H) 7.55 (m, 1 H) 7.67 (d, *J*=7.72 Hz, 1 H) 8.37 (dd, *J*=7.72, 1.84 Hz, 1 H) 8.55 (dd, *J*=4.78, 1.84 Hz, 1 H) 15.72 (s, 1 H).

Example 159

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,5-naphthyridin-2(1H)-
one

Example 159A2H-pyrido[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared as a minor bi-product (0.50 g, 4 %) from 2,3-pyridinecarboxylic anhydride (11.4 g, 76 mmol) and trimethylsilyl azide (11.0 mL, 80 mmol) according to the procedure of Le Count, D.J. and co-workers described in *Synthesis*, 1982, 972-973. ¹H NMR (300 MHz, DMSO- d₆) δ 7.56 (dd, J=8.46, 1.47 Hz, 1 H) 7.71 (dd, J=8.46, 4.41 Hz, 1 H) 8.51 (dd, J=4.41, 1.47 Hz, 1 H) 11.78 (s, 1 H).

Example 159B1-butyl-2H-pyrido[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 159A for the product of Example 1A (0.12 g, 35%). ¹H NMR (300 MHz, DMSO- d₆) δ 0.92 (t, J=7.35 Hz, 3 H) 1.40 (m, J=15.26, 7.17 Hz, 2 H) 1.60 (m, 2 H) 3.98 (m, 2 H) 7.81 (dd, J=8.82, 4.41 Hz, 1 H) 7.97 (dd, J=8.64, 1.29 Hz, 1 H) 8.55 (dd, J=4.23, 1.29 Hz, 1 H).

Example 159C1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,5-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 159B for the product of Example 1B (0.053 g, 25%). MS (ESI-) m/z 397 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 0.94 (t, J=7.17 Hz, 3 H) 1.39 (m, 2 H) 1.54 (m, 2 H) 4.07 (t, J=7.72 Hz, 2 H) 7.28 (m, 2 H) 7.56 (m, 2 H) 7.68 (dd, J=7.91, 1.29 Hz, 1 H) 7.77 (d, J=8.46 Hz, 1 H) 8.39 (d, J=4.04 Hz, 1 H) 16.15 (s, 1 H).

Example 1601-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,5-naphthyridin-2(1H)-oneExample 160A1-benzyl-2H-pyrido[3,2-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 1B substituting the product of Example 159A for the product of Example 1A and substituting benzyl bromide for n-butyl bromide (0.92 g, 60%). ¹H NMR (300 MHz, DMSO- d₆) δ 5.28 (s, 2 H) 7.33 (m, 3 H) 7.43 (m, 2 H) 7.70 (m, 2 H) 8.54 (dd, J=3.86, 1.65 Hz, 1 H).

Example 160B

ethyl 1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate

The title compound was prepared according to the procedure of Example 89A substituting the product of Example 160A for the product of Example 1B (0.110 g, 23%).

5 MS (DCI) m/z 325 (M+H)⁺.

Example 160C

N-[2-(aminosulfonyl)phenyl]-1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamide

10 The title compound was prepared according to the procedure of Example 89B substituting the product of Example 160B for the product of Example 89A and 2-aminobenzenesulfonamide for 2-amino-4-chlorobenzenesulfonamide (0.12 g, 86%). MS (ESI-) m/z 449 (M-H)⁻.

Example 160D

15 1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,5-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 84C substituting the product of Example 160C for the product of Example 84B (0.120 g, 99%).
20 MS (ESI-) m/z 431 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 5.39 (s, 2 H) 7.25 (m, 7 H) 7.40 (dd, J=8.46, 4.41 Hz, 1 H) 7.57 (m, 2 H) 7.68 (d, J=8.09 Hz, 1 H) 8.35 (d, J=4.04 Hz, 1 H) 16.11 (s, 1 H).

Example 161

25 1-benzyl-4-chloro-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared from the product of Example 15B and phosphoryl chloride according to the procedure of Stadlbauer, W. and co-workers described in *Journal of Heterocyclic Chemistry*, 35, 1998, 627-636 (2.07 g, 88%). MS (ESI-) m/z 449 (M-H)⁻; ¹H
30 NMR (300 MHz, DMSO- d₆) δ 5.68 (s, 2 H) 7.29 (m, 6 H) 7.57 (m, 2 H) 7.75 (m, 1 H) 7.92 (dd, J=7.91, 1.29 Hz, 1 H) 8.56 (dd, J=8.09, 1.47 Hz, 1 H) 8.87 (dd, J=4.60, 1.65 Hz, 1 H) 12.73 (s, 1 H).

Example 162

35 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1E)-phenylmethylene]amino-2(1H)-quinolinone

Example 162A2-[(2E)-2-benzylidenehydrazino]benzoic acid

The title compound was prepared from 2-hydrazinobenzoic acid hydrochloride (1.89 g, 10.0 mmol) and benzaldehyde (1.06 g, 10.0 mmol) according to the procedure of Fischer, E. and co-workers described in *Chem. Ber.*, 35, 1902, 2318 (2.4 g, quantitative yield). MS (DCI) m/z 241 (M+H)⁺.

Example 162B1-[[[(1E)-phenylmethylene]amino]-2H-3,1-benzoxazine-2,4(1H)-dione

A solution of the product of Example 162A (1.2 g, 5.0 mmol) and potassium hydroxide (0.336 g, 6.0 mmol) in 15 ml of water at 0 °C was treated dropwise with 20% phosgene in toluene (3.5 ml, 6.5 mmol), stirred for 1 hour, treated with 1M NaOH to reach a pH of 10 and extracted 3 X 30 mL with ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried (Na₂SO₄), and concentrated to provide the title compound (0.32 g, 24%). MS (DCI) m/z 267 (M+H)⁺.

Example 162C3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[[[(1E)-phenylmethylene]amino]-2(1H)-quinolinone

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 162B for the product of Example 1B (0.110 g, 49%). MS (ESI-) m/z 443 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 7.16 (m, 1 H) 7.30 (m, 2 H) 7.54 (m, 6 H) 7.67 (dd, J=8.09, 1.47 Hz, 1 H) 7.99 (m, 2 H) 8.13 (dd, J=7.91, 1.29 Hz, 1 H) 9.04 (s, 1 H) 16.09 (s, 1 H).

Example 1631-amino-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2(1H)-quinolinone

A solution of the product of Example 162C (0.075 g, 0.17 mmol) in 10% aqueous potassium hydroxide (5 mL) was refluxed for 2 hours, cooled, treated with 12 M HCl to pH 3 which produced a precipitate. The solid was collected by filtration, washed repeatedly with water and dried to constant mass to give the desired product (0.050 g, 83%). MS (ESI-) m/z 355 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 5.31 (s, 2 H) 7.05 (t, J=8.09 Hz, 1 H) 7.27 (m, 2 H) 7.53 (m, 2 H) 7.67 (m, 2 H) 8.07 (dd, J=8.09, 1.47 Hz, 1 H) 16.38 (s, 1 H).

Example 164

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(2-phenylethyl)-1,8-naphthyridin-2(1H)-one

Example 164A

ethyl 2-[(2-phenylethyl)amino]nicotinate

The title compound was prepared according to the procedure of Example 3A substituting phenethylamine for 2-ethyl-butylamine (1.98 g, 73%). MS (DCI) m/z 271 (M+H)⁺.

Example 164B

1-(2-phenylethyl)-2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione

The title compound was prepared according to the procedure of Example 3B substituting the product of 164A for the product of Example 3A (0.53 g, 99%). MS (DCI) m/z 269 (M+H)⁺.

Example 164C

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(2-phenylethyl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 164B for the product of Example 1B (0.132 g, 59%). MS (ESI-) m/z 445 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 2.87 (m, 2 H) 4.47 (m, 2 H) 7.16 (dd, J=7.72, 4.78 Hz, 1 H) 7.29 (m, 7 H) 7.57 (m, 1 H) 7.67 (d, J=7.72 Hz, 1 H) 8.40 (dd, J=7.72, 1.84 Hz, 1 H) 8.57 (dd, J=4.78, 1.84 Hz, 1 H) 15.90 (s, 1 H).

Example 165

1-butyl-4-chloro-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 161 substituting the product of Example 1D for the product of Example 15B.

Example 166

4-amino-1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

A solution of the product of Example 165 (0.10 g, 0.24 mmol) and ammonia (2 ml of a 2 M solution in methanol, 4.0 mmol) was stirred in a sealed tube at 100°C for 2 hours, allowed to cool to room temperature. The resulting solid collected by filtration and washed

with methanol (2 ml) to give the title compound as a brown solid (0.019 g, 20%). MS (ESI-) m/z 396 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.94 (t, J=7.35 Hz, 3H), 1.38 (m, 2H), 1.66 (m, 2H), 4.44 (t, J=7.35 Hz, 2H), 7.48 (m, 2H), 7.55 (d, J=8.09 Hz, 1H), 7.70 (t, J=8.46 Hz, 1H), 7.84 (dd, J=7.72, 1.10 Hz, 1H), 8.77 (d, J=8.09 Hz, 1H), 8.82 (dd, J=4.78, 1.47 Hz, 1H), 9.84 (brs, 1H).

Example 167

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-(methylamino)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 166 substituting methylamine (2 M solution in methanol) for ammonia (2 M solution in methanol) as a brown solid (0.023 g, 23%). MS (ESI-) m/z 410 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.91 (t, J=7.17 Hz, 3H), 1.34 (m, 2H), 1.60 (m, 2H), 2.95 (d, J=5.15 Hz, 3H), 4.31 (m, J=7.36 Hz, 2H), 7.36 (dd, J=8.09, 4.78 Hz, 1H), 7.40 (d, J=8.46 Hz, 1H), 7.49 (t, J=8.09 Hz, 1H), 7.71 (m, 2H), 7.85 (dd, J=7.91, 1.29 Hz, 1H), 8.56 (dd, J=8.27, 1.29 Hz, 1H), 8.69 (dd, J=4.60, 1.29 Hz, 1H), 12.44 (brs, 1H).

Example 168

1-butyl-4-(dimethylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 166 substituting dimethylamine (2 M solution in methanol) for ammonia (2 M solution in methanol) as a brown solid (0.015 g, 15%). MS (ESI-) m/z 424 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.93 (t, J=7.35 Hz, 3H), 1.36 (m, 2H), 1.63 (m, 2H), 2.99 (s, 6H), 4.36 (t, J=7.72 Hz, 2H), 7.38 (m, 2H), 7.51 (m, 1H), 7.73 (m, 1H), 7.88 (dd, J=8.09, 1.47 Hz, 1H), 8.36 (dd, J=8.09, 1.47 Hz, 1H), 8.71 (dd, J=4.78, 1.84 Hz, 1H), 12.45 (s, 1H).

Example 169

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydrazino-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 166 substituting hydrazine for ammonia (2 M solution in methanol) as a brown solid (0.026 g, 26%). MS (ESI-) m/z 411 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.94 (t, J=7.35 Hz, 3H), 1.39 (m, 2H), 1.64 (m, 2H), 3.35 (brs, 3H), 4.41 (t, J=7.72 Hz, 2H), 7.04 (t, J=7.54 Hz, 1H), 7.42 (dd, J=7.72, 4.78 Hz, 1H), 7.57 (m, 1H), 7.83 (dd, J=7.91, 1.65 Hz, 1H), 8.49 (dd, J=7.72, 1.84 Hz, 1H), 8.64 (d, J=8.46 Hz, 1H), 8.68 (dd, J=4.78, 1.84 Hz, 1H), 9.65 (s, 1H).

Example 1704-azido-1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

A solution of the product of Example 165 (0.1 g, 0.24 mmol) and sodium azide (0.037 g, 0.571 mmol) in dimethylformamide (2.5 ml) was stirred at 80°C for 1.5 hours, allowed to cool to room temperature and concentrated under reduced pressure. The crude residue was purified by a C8 HPLC column eluting with 20% to 80% acetonitrile in water with 1% trifluoroacetic acid to give the title compound (0.025 g, 26% after column purification). MS (ESI-) m/z 422 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.94 (t, J=7.35 Hz, 3H), 1.38 (m, 2H), 1.67 (m, 2H), 4.42 (t, J=7.54 Hz, 2H), 7.41 (d, J=7.72 Hz, 1H), 7.46 (dd, J=7.91, 4.60 Hz, 1H), 7.56 (m, 1H), 7.76 (m, 1H), 7.91 (dd, J=8.09, 1.10 Hz, 1H), 8.41 (dd, J=8.09, 1.84 Hz, 1H), 8.84 (dd, J=4.41, 1.84 Hz, 1H), 12.74 (s, 1H).

Example 1711-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-[(2-hydroxyethyl)amino]-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 166 substituting ethanolamine (0.25 g, 4.0 mmol) and anhydrous methanol (2 ml) for ammonia (2 M solution in methanol) (0.02 g, 19%). MS (ESI-) m/z 440 (M-H)-; ¹H NMR (300 MHz, DMSO- d₆) δ 0.92 (t, J=7.35 Hz, 3H), 1.35 (m, 2H), 1.61 (m, 2H), 2.71 (m, 1H), 3.40 (m, 1H), 3.47 (m, 2H), 3.57 (m, 2H), 4.32 (t, J=7.36 Hz, 2H), 7.35 (m, 1H), 7.39 (d, J=6.99 Hz, 1H), 7.44 (t, J=7.72 Hz, 1H), 7.51 (brs, 1H), 7.67 (m, 1H), 7.81 (dd, J=7.91, 1.29 Hz, 1H), 8.66 (dd, J=8.09, 1.47 Hz, 1H), 8.69 (dd, J=4.78, 1.47 Hz, 1H).

Example 1723-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-propoxyquinolin-2(1H)-oneExample 172Aethyl 2-(hydroxyamino)benzoate

The title compound is prepared from ethyl-2-nitrobenzoate according to the procedure of Entwistle and Gilkerson described in *Tetrahedron*, 34, 1978, 213-215.

Example 172Bethyl 2-(propoxyamino)benzoate

The title compound is prepared according to the procedure of Example 1B substituting the product of Example 172A for the product of Example 1A and substituting n-propyl bromide for n-butyl bromide.

Example 172Cethyl 2-[(3-ethoxy-3-oxopropanoyl)(propoxy)amino]benzoate

The title compound is prepared according to the procedure of Example 157B
5 substituting the product of Example 172B for the product of Example 157A.

Example 172Dethyl 4-hydroxy-2-oxo-1-propoxy-1,2-dihydroquinoline-3-carboxylate

The title compound is prepared according to the procedure of Example 157C
10 substituting the product of Example 172C for the product of Example 157B.

Example 172EN-[2-(aminosulfonyl)phenyl]-4-hydroxy-2-oxo-1-propoxy-1,2-dihydroquinoline-3-carboxamide

15 The title compound is prepared according to the procedure of Example 84C substituting the product of Example 172D for the product of Example 84B and substituting 2-aminosulfonamide for the product of Example 84A.

Example 172F

20 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-propoxyquinolin-2(1H)-one

The title compound is prepared according to the procedure of Example 84D substituting the product of Example 172E for the product of Example 84C. The sodium salt of the title compound is prepared according to the procedure of Example 1D.

Example 173

25 7-benzyl-5-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-(hydroxymethyl)-7,7a-dihydrothienof[2,3-b]pyridin-6(3aH)-one

Example 173Amethyl 2-amino-4-(hydroxymethyl)thiophene-3-carboxylate

30 A solution of methyl cyanoacetate (1.18 mL, 13.28 mmol) and sodium sulfide nonahydrate (3.20 g, 13.28 mmol) in methanol (25 mL) at 0 °C was treated with 1-acetoxy-3-chloroacetone (2.0 g, 13.28 mmol). The cold bath was removed and triethylamine (1.86 mL, 13.28 mmol) was added dropwise. The solution was stirred at room temperature for 20 hours then diluted with water and extracted into ethyl acetate. The organic layer was dried over
35 sodium sulfate, filtered, and the solvent removed under vacuum to provide the titled compound (1.25 g, 51%). MS (DCI/NH₃) m/z 188 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 3.68 (s, 3 H) 4.45 (dd, J=5.52, 1.47 Hz, 2 H) 4.88 (t, J=5.70 Hz, 1 H) 6.12 (s, 1 H) 7.28 (s,

2 H)

Example 173B

5 methyl 2-amino-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)thiophene-3-carboxylate

A solution of the product of Example 173A (1.25g, 6.70 mmol) and N,N-diisopropylethylamine (0.71 mL, 7.35 mmol) in dichloromethane at 0 °C was treated with *t*-butyldimethylsilyl trifluoromethanesulfonate (0.85 mL, 6.70 mmol). After stirring at 0 °C for 1 hour, the solution was poured into water, extracted into dichloromethane, and dried over sodium sulfate. The solvent was removed under vacuum to provide the titled compound (0.87 g, 78%). MS (DCI/NH₃) *m/z* 302 (M+H)⁺; ¹H NMR (300 MHz, DMSO- *d*₆) δ 0.00 (m, 6 H) 0.84 (s, 9 H) 3.62 (s, 3 H) 4.59 (d, *J*=1.47 Hz, 2 H) 6.03 (m, 1 H) 7.22 (s, 2 H).

Example 173C

15 methyl 2-(benzylamino)-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)thiophene-3-carboxylate

A solution of the product of Example 173B (0.36 g, 1.20 mmol) and potassium carbonate (0.185 g, 1.30 mmol) in acetonitrile (5 mL) was treated with benzyl bromide (0.16 mL, 1.25 mmol) at 45 °C for 24 hours. The solution was poured into water and extracted into ethyl acetate (2X). The combined organic layers were concentrated and purified by flash chromatography eluting with dichloromethane to provide the titled compound (0.17 g, 36%). MS (DCI/NH₃) *m/z* 392 (M+H)⁺; ¹H NMR (300 MHz, DMSO- *d*₆) δ 0.00 (m, 6 H) 0.84 (s, 9 H) 3.67 (m, 3 H) 4.38 (d, *J*=5.88 Hz, 2 H) 4.62 (d, *J*=1.47 Hz, 2 H) 6.12 (s, 1 H) 7.28 (m, 5 H) 8.16 (t, *J*=6.07 Hz, 1 H).

Example 173D

25 1-benzyl-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione

The title compound was prepared according to the procedure of Example 3B substituting the product of Example 173C for the product of Example 3A (0.015 g, 83%). MS (DCI/NH₃) *m/z* 404 (M+H)⁺

Example 173E

35 7-benzyl-5-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-3-(hydroxymethyl)-7,7*A*-dihydrothieno[2,3-*b*]pyridin-6(3*AH*)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 173D for the product of Example 1B. (0.013 g, 8%). MS

(DCI/NH₃) m/z 468 (M+H)⁺; ¹H NMR (300 MHz, DMSO- d₆) δ 4.78 (s, 2 H) 5.42 (s, 2 H) 7.13 (s, 1 H) 7.32 (m, 5 H) 7.53 (t, J=7.17 Hz, 1 H) 7.64 (d, J=9.93 Hz, 1 H) 7.75 (m, 1 H) 7.91 (d, J=6.99 Hz, 1 H).

Example 174

5 1-benzyl-3-(6-chloro-1,1-dioxido-4*H*-thieno[3,2-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one

Example 174A

3-amino-5-chlorothiophene-2-sulfonamide

10 The title compound is prepared according to the procedure of Hansen, J. and coworkers as described in J. of Medicinal Chemistry 2002, 45, 4171-4187.

Example 174B

15 *N*-[2-(aminosulfonyl)-5-chlorothien-3-yl]-1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide

The title compound is prepared according to the procedure of Example 84C substituting the product of Example 174A for the product of Example 84A and substituting 3-amino-5-chlorothiophene-2-sulfonamide for 2-amino-5-bromobenzenesulfonamide.

20 Example 174C

1-benzyl-3-(6-chloro-1,1-dioxido-4*H*-thieno[3,2-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1*H*)-one

The title compound is prepared according to the procedure of Example 84D substituting the product of Example 174B for the product of Example 84C.

25 Example 175

1-benzyl-3-(6-chloro-1,1-dioxido-4*H*-thieno[3,2-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one

Example 175A

30 *N*-[2-(aminosulfonyl)-5-chlorothien-3-yl]-1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide

The title compound is prepared according to the procedure of Example 84C substituting the product of Example 174A for the product of Example 84A and substituting the product of Example 99A for the product of example Example 84B.

35 Example 175B

1-benzyl-3-(6-chloro-1,1-dioxido-4*H*-thieno[3,2-*e*][1,2,4]thiadiazin-3-yl)-4-hydroxyquinolin-

2(1H)-one

The title compound is prepared according to the procedure of Example 84D substituting the product of Example 175A for the product of Example 84C.

Example 1763-[5-(aminomethyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-benzyl-4-hydroxy-1,8-naphthyridin-2(1H)-one

The product of Example 97 (91.6 mg, 0.2002 mmol) and Raney-nickel (0.94 g) in tetrahydrofuran (92 mL) and triethylamine (4.5 mL) was hydrogenated at 60 psi H₂ pressure at 50° for 2 days, with additional Raney-nickel (0.94 g) being added after 24 hrs. The reaction was cooled to room temperature, filtered, and concentrated by rotary evaporation to a greenish-yellow solid. The residue was purified by preparative HPLC on a Waters Symmetry C8 column (40mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 12min (15min run time) at a flow rate of 70mL/min to give the title compound as a white solid (11 mg, 12%). MS (ESI)⁻ m/z 460 (M-H)⁻; ¹H NMR (300 MHz, DMSO- d₆) δ 4.31 (s, 2 H) 5.64 (s, 2 H) 7.28 (m, 6 H) 7.49 (m, 1 H) 7.74 (d, J=7.35 Hz, 1 H) 7.85 (d, J=7.72 Hz, 1 H) 8.48 (m, 3 H) 8.68 (m, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 4.16 (s, 2 H) 5.54 (s, 2 H) 7.24 (m, 7 H) 7.65 (d, J=7.72 Hz, 2 H) 8.43 (dd, J=7.54, 1.65 Hz, 1 H) 8.50 (dd, J=4.41, 1.84 Hz, 1 H).

Example 1778-benzyl-3-chloro-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxypyrido[2,3-c]pyridazin-7(8H)-oneExample 177A3-(benzylamino)-6-chloropyridazine-4-carboxylic acid

2,5-Dichloro-pyridazine-3-carboxylate (0.40 g, 2.07 mmol) in toluene (8 mL) was reacted with triethylamine (0.72 mL, 5.20 mmol) and benzyl amine (0.23 mL, 2.07 mmol) at 90 °C for 8 hours. The solution was partitioned between water and ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated to yield the title compound (0.257 g, 47%). MS (DCI/NH₃) m/z 264 (M+H)⁺.

Example 177B8-benzyl-3-chloro-5H-pyridazino[3,4-d][1,3]oxazine-5,7(8H)-dione

The title compound is prepared according to the procedure of Example 108C substituting the product of Example 177A for the product of Example 108B.

Example 177C

8-benzyl-3-chloro-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxypyrido[2,3-c]pyridazin-7(8H)-one

The title compound is prepared according to the procedure of Example 1D substituting the product of Example 177B for the product of Example 1B.

Example 178

8-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxy-3-(methylthio)pyrido[2,3-c]pyridazin-7(8H)-one

The product of Example 177 is reacted with methanethiol in toluene at elevated temperatures the reaction was concentrated give the title compound.

Example 179

8-benzyl-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-5-hydroxypyrido[2,3-c]pyridazin-7(8H)-one

The title compound is produced by the procedure of Example 109 substituting the product of Example 178 for the product of Example 108D.

Example 180

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,6-naphthyridin-2(1H)-one

Example 180A

methyl 4-(benzylamino)nicotinate

The title compound is prepared from 3-carbomethoxy-4-chloropyridine and benzylamine according to the procedure of Winn, et.al. as described in *J. Med. Chem.*, **36**, 1993, 2676-2688.

Example 180B

1-benzyl-2H-pyrido[4,3-d][1,3]oxazine-2,4(1H)-dione

The title compound is prepared according to the procedure of Example 3B substituting the product of Example 180A for the product of Example 3A.

Example 180C

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,6-naphthyridin-2(1H)-one

The title compound is prepared according to the procedure of Example 1D substituting the product of Example 180B for the product of Example 1B.

Example 181

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,7-naphthyridin-2(1H)-one

Example 181A

2H-pyrido[3,4-d][1,3]oxazine-2,4(1H)-dione

The title compound is prepared according to the procedure of Example 110A from 3-aminoisonicotinic acid.

Example 181B

1-benzyl-2H-pyrido[3,4-d][1,3]oxazine-2,4(1H)-dione

The title compound is prepared according to the procedure of Example 1B substituting the product of Example 181A for the product of Example 1A, substituting DMF for DMA, and substituting benzyl bromide for n-butyl bromide, respectively.

Example 181C

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,7-naphthyridin-2(1H)-one

The title compound is prepared according to the procedure of Example 1D substituting the product of Example 181C for the product of Example 1B.

Example 182

1-(benzylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

A slurry of the product of Example 162 (0.133 g, 0.3 mmol) and 10% palladium on carbon (0.02 g, catalytic amount) in THF (25 mL) was hydrogenated under 1 atmosphere of hydrogen for 4 hours, filtered through Celite and the filtrate was concentrated. The residue was slurried in 1 mL DMSO / 5 mL MeOH for 15 minutes and the solid was collected by filtration and dried under vacuum to give the title compound (0.08 g, 60%). MS (ESI-) m/z 445 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d₆) δ 3.93 (s, 2 H) 6.09 (t, J=6.99 Hz, 1 H) 7.09 (t, J=7.35 Hz, 1 H) 7.35 (m, 5 H) 7.54 (m, 4 H) 7.69 (t, J=8.82 Hz, 2 H) 8.10 (dd, J=7.91, 1.29 Hz, 1 H) 16.28 (s, 1 H).

Example 183A

2-amino-5-methoxybenzenesulfonamide

The title compound was prepared from 4-methoxyaniline using the procedure described in *Journal of the Chemical Society, Perkin 1*, 1979, 1043.

Example 183B

Ethyl (7-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

To a solution of the product of Example 183A (0.534 g, 2.64 mmol) and triethylamine (0.44 mL, 3.17 mmol) in anhydrous dichloromethane (8 mL) under nitrogen at 0°C was added dropwise ethyl malonyl chloride (0.39 mL, 3.04 mmol). The resulting mixture was stirred at 25°C for 6 hours. The reaction mixture was diluted with 1 N HCl (30 mL), and the aqueous layer was extracted with ethyl acetate (2 X 30 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated and the resulting brown solid was recrystallized from dichloromethane/methanol to give a pink solid (420 mg). The solid was treated with anhydrous sodium carbonate (700 mg, 6.65 mmol) in anhydrous ethanol (15 mL) and heated at reflux for 7 hours. The solid was filtered off, and the filtrate was concentrated to give the title compound as a white solid (420 mg, total yield for two steps 50%). MS (ESI) m/z 297 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.19 (t, J=7.17 Hz, 3 H) 3.23 (s, 2 H) 3.75 (s, 3 H) 4.07 (q, J=6.99 Hz, 2 H) 6.99 (m, 3 H).

Example 183C

4-hydroxy-3-(7-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

To a solution of the product of Example 183B (0.5 g, 1.6 mmol) and the product of Example 12A (0.375 g, 1.6 mmol) in anhydrous THF (16 mL) under nitrogen at 0°C was added sodium hydride (95%, 0.162 g, 6.4 mmol). The reaction was heated at reflux for 4 hours, cooled to 0°C, and treated dropwise with glacial acetic acid (3 mL). The resulting mixture was heated at reflux for 2 hours, cooled to 25°, and diluted with ice water (150 mL). The resulting precipitate was collected by filtration, washed with water and recrystallized from dioxane/water to give the title compound (566 mg, 80%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) m/z 441 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 3.82 (s, 3 H) 4.29 (m, 2 H) 7.16 (m, 4 H) 8.36 (dd, J=7.54, 2.02 Hz, 1 H) 8.52 (dd, J=4.60, 2.02 Hz, 1 H) 15.86 (s, 1 H).

Example 184

4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 183C (0.027 g, 0.061 mmol) in dichloromethane (0.6 mL) was reacted with boron tribromide (1.0 M, 0.37 mL, 0.37 mmol) in dichloromethane at 25°C for 18 hours. The reaction was quenched with methanol and stirred for 30 minutes at 25°C. The reaction was concentrated under reduced pressure to give the title compound as a solid (20.4 mg, 78%). The disodium salt of the title compound was prepared according to the procedure of Example 1D using two equivalents of sodium hydroxide. MS (ESI-) m/z 427 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 4.29 (m, 2 H) 6.51 (m, 2 H) 6.78 (m, 1 H) 7.09 (dd, J=7.72, 4.78 Hz, 1 H) 8.34 (dd, J=7.35, 1.84 Hz, 1 H) 8.48 (dd, J=4.60, 2.02 Hz, 1 H) 15.23 (br s, 1 H).

Example 185

(3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy)acetonitrile

The product of Example 184 (0.050 g, 0.12 mmol) in N,N-dimethylformamide (1 mL) was reacted with 2-bromoacetonitrile (14 μL, 0.2 mmol), potassium carbonate (0.029 g, 0.22 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 30 hours. The reaction mixture was diluted with water (50 mL) and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was triturated with hexanes and dichloromethane to give the title compound as a pale yellow solid (16.8 mg, 30%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. (ESI-) m/z 466 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 4.29 (m, 2 H) 5.27 (s, 2 H) 7.13 (dd, J=7.72, 4.78 Hz, 1 H) 7.31 (m, 3 H) 8.36 (dd, J=7.72, 1.84 Hz, 1 H) 8.53 (dd, J=4.78, 1.84 Hz, 1 H) 15.99 (s, 1 H).

Example 186

3-(1,1-dioxido-7-propoxy-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (0.030 g, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with 1-bromopropane (0.025 mL, 0.28 mmol), potassium carbonate (60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized from dichloromethane:hexanes to give the title compound (14 mg, 43%). The sodium salt of the

title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 0.99 (t, J=7.35 Hz, 3 H) 1.48 (m, 2 H) 1.75 (m, 3 H) 3.98 (t, J=6.43 Hz, 2 H) 4.29 (m, 2 H) 7.16 (m, 4 H) 8.36 (dd, J=7.72, 1.84 Hz, 1 H) 8.52 (dd, J=4.60, 2.02 Hz, 1 H) 15.85 (s, 1 H). (ESI-) m/z 469 (M-H).

5

Example 187

4-hydroxy-3-[7-(methoxymethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (30mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with bromo(methoxy)methane (0.021 mL, 0.28 mmol), potassium carbonate (38 mg, 0.28 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.98 (d, J=6.62 Hz, 6 H) 1.56 (m, 2 H) 1.70 (m, 1 H) 3.42 (s, 3 H) 4.47 (m, 2 H) 5.31 (s, 2 H) 7.44 (m, 3 H) 7.66 (m, 1 H) 8.54 (d, J=8.09 Hz, 1 H) 8.85 (s, 1 H). (ESI-) m/z 471 (M-H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

20

Example 188

4-Hydroxy-1-(3-methylbutyl)-3-[7-[(2-methylprop-2-enyl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1,8-naphthyridin-2(1H)-one

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with 3-bromo-2-methylprop-1-ene (8 μL, 0.077 mmol), potassium carbonate (60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 24 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized from dichloromethane:hexanes to give the title compound (17.4 mg, 50%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 1.78 (s, 3 H) 4.29 (m, 2 H) 4.54 (s, 2 H) 4.98 (s, 1 H) 5.08 (s, 1 H) 7.12 (m, 2 H) 7.22 (m, 2 H) 8.36 (dd, J=7.54, 2.02 Hz, 1 H) 8.52 (dd, J=4.60, 2.02 Hz, 1 H) 15.86 (s, 1H). (ESI-) m/z 481 (M-H).

35

Example 189

tert-butyl (1-[3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-

dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetate

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with *tert*-butyl bromoacetate (0.04 mL, 0.28 mmol), potassium carbonate (0.04 g, 0.28 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 24 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound (20 mg, 53%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.97 (d, J=6.62 Hz, 6 H) 1.43 (s, 9 H) 1.51 (m, 2 H) 1.66 (m, 1 H) 4.35 (m, 2 H) 4.77 (s, 2 H) 7.33 (m, 4 H) 8.42 (d, J=8.09 Hz, 1 H) 8.63 (s, 1 H). (ESI-) m/z 541 (M-H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D.

Example 1902-({3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with 2-bromoacetamide (16 mg, 0.12 mmol), potassium carbonate 24 mg, 0.17 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 48 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was triturated with dichloromethane:hexanes to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 4.29 (m, 2 H) 4.49 (s, 2 H) 7.13 (m, 2 H) 7.24 (m, 2 H) 7.40 (m, 1 H) 7.62 (m, 1 H) 8.36 (dd, J=7.54, 2.02 Hz, 1 H) 8.52 (dd, J=4.60, 2.02 Hz, 1 H) 15.89 (s, 1 H). (ESI-) m/z 484 (M-H)⁺.

Example 1913-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with (bromomethyl)benzene (0.0138 mL, 0.11 mmol), cesium carbonate (50 mg, 0.15 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and

concentrated under reduced pressure. The resulting residue was triturated with ethyl acetate to give the title compound (13 mg, 36%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.25 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 4.29 (m, 2 H) 5.17 (s, 2 H) 7.12 (dd, J=7.72, 4.78 Hz, 1 H) 7.23 (m, 3 H) 7.41 (m, 5 H) 8.36 (dd, J=7.35, 1.84 Hz, 1 H) 8.52 (dd, J=4.78, 1.84 Hz, 1 H) 15.87 (s, 1 H). (ESI-) m/z 517 (M-H)⁺.

Example 192

3-[1,1-dioxido-7-(2-pyrrolidin-1-ylethoxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with 1-(2-chloroethyl)pyrrolidine hydrochloride (19 mg, 0.11 mmol), potassium carbonate (96 mg, 0.69 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 72 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 5% methanol/dichloromethane to give the title compound. The potassium salt of the title compound was prepared according to the procedure of Example 1D substituting potassium hydroxide for sodium hydroxide. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 1.91 (m, 4 H) 3.16 (m, 4 H) 3.47 (m, 1 H) 4.30 (m, 4 H) 7.13 (dd, J=7.54, 4.60 Hz, 1 H) 7.24 (m, 3 H) 8.36 (dd, J=7.72, 1.84 Hz, 1 H) 8.53 (dd, J=4.60, 2.02 Hz, 1 H) 15.90 (s, 1 H). (ESI-) m/z 524 (M-H)⁺.

Example 193

3-[1,1-dioxido-7-(2-oxo-2-phenylethoxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide (1 mL) was reacted with 2-bromo-1-phenylethanone (30 mg, 0.15 mmol), potassium carbonate (60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with 0.2% methanol/dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR

(300 MHz, DMSO- d_6) δ ppm 0.96 (d, J =6.62 Hz, 6 H) 1.48 (m, 2 H) 1.65 (m, 1 H) 4.31 (m, 2 H) 5.70 (s, 2 H) 7.14 (m, 1 H) 7.24 (d, J =9.93 Hz, 3 H) 7.59 (t, J =7.35 Hz, 2 H) 7.71 (t, J =7.35 Hz, 1 H) 8.05 (m, 2 H) 8.38 (dd, J =7.91, 1.65 Hz, 1 H) 8.54 (m, 1 H) 15.85 (s, 1 H). (ESI-) m/z 545 (M-H)⁺.

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Example 194

3-[7-(allyloxy)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one

The product of Example 184 (30 mg, 0.07 mmol) in *N,N*-dimethylformamide (1 mL) was reacted with 3-iodoprop-1-ene (0.007 mL, 0.077 mmol), potassium carbonate 60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was triturated with hexanes to give the title compound. ¹H NMR (300 MHz, DMSO- d_6) δ ppm 0.98 (d, J =6.25 Hz, 6 H) 1.55 (m, 2 H) 1.68 (m, 1 H) 4.42 (m, 2 H) 4.69 (d, J =5.52 Hz, 2 H) 5.30 (dd, J =10.66, 1.47 Hz, 1 H) 5.43 (dd, J =17.28, 1.84 Hz, 1 H) 6.06 (m, 1 H) 7.29 (m, 3 H) 7.53 (m, 1 H) 8.49 (d, J =6.62 Hz, 1 H) 8.76 (m, 1 H) 15.29 (brs, 1H). (ESI-) m/z 467 (M-H)⁺.

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Example 195

4-Hydroxy-3-(7-isobutoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one

The product of Example 184 (30 mg, 0.07 mmole) in *N,N*-dimethylformamide (1 mL) was reacted with 1-bromo-2-methylpropane (0.034 mL, 0.3 mmol), potassium carbonate (60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue recrystallized from hexanes:dichloromethane to give the title compound (10.5 mg, 31%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d_6) δ ppm 0.96 (d, J =6.25 Hz, 6 H) 0.99 (d, J =6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 2.03 (m, 1 H) 3.80 (d, J =6.62 Hz, 2 H) 4.29 (m, 2 H) 7.15 (m, 4 H) 8.36 (dd, J =7.72, 1.84 Hz, 1 H) 8.52 (dd, J =4.78, 1.84 Hz, 1 H) 15.85 (s, 1 H). (ESI-) m/z 483 (M-H)⁺.

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Example 196

4-({3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)butanenitrile

The product of Example 184 (30 mg, 0.07 mmol) in N,N-dimethylformamide 1 mL) was reacted with 4-bromobutanenitrile (0.0154 mL, 0.15 mmol), potassium carbonate (60 mg, 0.42 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 96 hours. The reaction mixture was diluted with water and acidified to pH 5 with concentrated acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was recrystallized with hexanes:dichloromethane to give the title compound (21.8 mg, 62%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.62 (m, 1 H) 2.04 (m, 2 H) 2.68 (t, J=7.17 Hz, 2 H) 4.10 (t, J=5.88 Hz, 2 H) 4.29 (m, 2 H) 7.17 (m, 4 H) 8.36 (dd, J=7.91, 1.29 Hz, 1 H) 8.52 (dd, J=4.60, 1.65 Hz, 1 H) 15.88 (s, 1 H). (ESI-) m/z 494 (M-H).

Example 197

(({3-[1-(3-methylbutyl)-4-oxido-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetate

The product of Example 189 (15 mg, 0.028 mmol) in a mixture of trifluoroacetic acid (0.8 mL) and dichloromethane (0.2 mL) was stirred for two hours at 25°C. The solvents were removed under reduced pressure to give a yellow solid that was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (2 X 20 mL). The aqueous layer was acidified to pH 2 with 1N HCl and extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the title compound as a white solid (8 mg, 62%). The disodium salt was prepared according to the procedure of Example 1D using two equivalents of sodium hydroxide. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.99 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.70 (m, 1 H) 3.17 (s, 1 H) 4.49 (m, 2 H) 4.88 (s, 2 H) 7.36 (m, 2 H) 7.49 (m, 1 H) 7.70 (d, J=9.56 Hz, 1 H) 8.56 (dd, J=7.91, 1.65 Hz, 1 H) 8.88 (d, J=2.94 Hz, 1 H). (ESI-) m/z 485 (M-H).

Example 198

3-[7-(2-aminoethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A solution of the product of Example 185 (21.8 mg, 62%) in anhydrous tetrahydrofuran (0.5 mL) was treated with LiBH₄ (10 mg, 0.46 mmol), stirred at ambient

temperature for 16 hours, diluted with water (30 mL) and extracted with ethyl acetate (2 X 30 mL). The combined organic layers were washed with water, brine and dried over anhydrous magnesium sulfate. The slurry was filtered and the solvent removed under reduced pressure yielding the title compound as a yellow solid (10.1 mg, 97%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 2.82 (m, 2 H) 4.13 (t, J=5.33 Hz, 2 H) 4.29 (m, 2 H) 5.40 (m, 2 H) 7.17 (m, 4 H) 8.36 (dd, J=7.72, 1.84 Hz, 1 H) 8.52 (dd, J=4.60, 2.02 Hz, 1 H) 15.88 (s, 1 H). (ESI-) m/z 470 (M-H)⁺.

Example 199

2-((3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)-N-methylacetamide

A mixture of Example 197 (4.7 mg, 0.0097 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.4 mg, 0.01 mmol), methylamine in tetrahydrofuran (2.0 M, 10 μL, 0.02 mmol) and 1-hydroxybenzotriazole (1.4 mg, 0.01 mmol) in N,N-dimethylformamide (0.2 mL) was stirred at 25°C for 5 hours. The reaction mixture was diluted with ethyl acetate (40 mL), washed with saturated sodium bicarbonate, water and brine, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent removed under reduced pressure to give the title compound as a pale yellow solid (4 mg, 83%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 2.67 (d, J=4.78 Hz, 3 H) 4.30 (m, 2 H) 4.53 (s, 2 H) 7.18 (m, 4 H) 8.11 (m, 1 H) 8.36 (dd, J=7.54, 2.02 Hz, 1 H) 8.52 (dd, J=4.78, 1.84 Hz, 1 H) 15.90 (s, 1 H). (ESI-) m/z 498 (M-H)⁺.

Example 200

3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl acetate

A mixture of Example 184 (30 mg, 0.07 mmol), triethylamine (12 μL, 0.084 mmol) and acetic anhydride (8 μL, 0.084 mmol) in anhydrous dichloromethane (1 mL) was stirred at 25°C for 16 hours. The reaction mixture was diluted with ethyl acetate and water, acidified to pH 5 with acetic acid and partitioned. The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with saturated sodium bicarbonate, water, brine, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure to give the title compound as a white solid (29.5 mg, 89%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.98 (d, J=6.25 Hz, 6 H) 1.56 (m, 2 H) 1.69 (m, 1 H) 2.30 (s, 3 H) 4.46 (m, 2 H) 7.44 (m, 1 H) 7.52 (d, J=8.82 Hz, 1 H) 7.72 (m, 2 H) 8.53 (dd,

J=7.72, 1.47 Hz, 1 H) 8.83 (s, 1 H). (ESI-) m/z 469 (M-H)⁻.

Example 201

3-[1,1-dioxido-7-(pyridin-2-yloxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (10 mg, 0.023 mmol) was reacted with 2-bromopyridine (2.4 μ L, 0.025 mmol), cesium carbonate (15 mg, 0.046 mmol) and copper metal (40 mg) in dimethylsulfoxide (0.1 mL) at 110°C in a microwave reactor for 2 hours. The mixture was cooled to 25°C, poured into water (20 mL) and extracted with ethyl acetate (2 X 20 mL).

The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure leaving a tan solid. The solid was chromatographed on silica gel, eluting first with methylene chloride, then 1% methanol in methylene chloride gave the title compound as a light brown solid (5 mg, 42%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (s, 3 H) 0.98 (s, 3 H) 1.48 (m, 2 H) 1.65 (m, 1 H) 4.30 (t, J=7.50 Hz, 2 H) 7.14 (m, 3 H) 7.35 (s, 3 H) 7.89 (m, 1 H) 8.17 (m, 1 H) 8.38 (dd, J=7.72, 2.21 Hz, 1 H) 8.53 (dd, J=4.78, 1.84 Hz, 1 H) 16.07 (s, 1 H). (ESI-) m/z 504 (M-H)⁻.

Example 202

3-[1,1-dioxido-7-(pyrimidin-2-yloxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 184 (10 mg, 0.023 mmole) was reacted with 2-bromopyrimidine (4.5 mg, 0.028 mmole), cesium carbonate (15 mg, 0.046 mmole) and tetrabutylammonium iodide (1 mg) in dimethylsulfoxide (0.1 mL) in a microwave reaction apparatus at 110°C for 1 hour. The mixture was cooled to 25°C, poured into water (20 mL) and extracted with ethyl acetate (2 X 50 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure leaving a tan solid. The solid was chromatographed on silica gel, eluting first with methylene chloride, followed by 2% methanol in methylene chloride, affording the title compound as a white solid (6 mg, 51%). The sodium salt of the title compound was prepared according to the procedure as described in Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (s, 3 H) 0.98 (s, 3 H) 1.48 (m, 2 H) 1.65 (m, 1 H) 4.30 (t, J=7.50 Hz, 2H) 7.14 (dd, J=7.54, 4.60 Hz, 1 H) 7.30 (t, J=4.78 Hz, 1 H) 7.42 (m, 3 H) 8.38 (dd, J=7.72, 1.84 Hz, 1 H) 8.54 (dd, J=4.78, 1.84 Hz, 1 H) 8.67 (s, 1 H) 8.68 (s, 1 H) 16.10 (s, 1 H). (ESI-) m/z 505 (M-H)⁻.

Example 203

2-({3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)-N,N-dimethylacetamide

The title compound was prepared according to the procedure of Example 185 substituting 2-chloro-N,N-dimethylacetamide for 2-bromoacetonitrile. The compound was purified by trituration with methanol. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 2.86 (s, 3 H) 3.01 (s, 3 H) 4.30 (m, 2 H) 4.90 (s, 2 H) 7.16 (m, 4 H) 8.36 (dd, J=7.72, 1.84 Hz, 1 H) 8.52 (d, J=4.78 Hz, 1 H) 15.86 (s, 1 H). (ESI-) m/z 512 (M-H)⁻.

Example 204

4-hydroxy-1-(3-methylbutyl)-3-(7-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The product of Example 12B (0.229g, 0.56 mmol) at 0°C was reacted with ammonium nitrate (0.058g, 0.72 mmol) in concentrated sulfuric acid (1.5 mL), stirred at 0°C for 30 minutes. The reaction mixture was poured onto crushed ice and the pH was adjusted to 9 with aqueous sodium hydroxide. The resulting solid was isolated by filtration to give the title compound (0.21 g, 81%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. (ESI-) m/z 456 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 4.29 (m, 2 H) 7.14 (m, 1 H) 7.52 (m, 1 H) 8.40 (m, 3 H) 8.54 (m, 1 H) 16.77 (s, 1 H).

Example 205 RZ

3-(7-amino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 204 (0.198 g, 0.43 mmol), iron powder (0.121g, 2.16 mmol), and NH₄Cl (0.031g, 0.58 mmol) in methanol:tetrahydrofuran:water (3:3:1,7mL) was stirred at reflux for nine hour. The reaction mixture was cooled to 25°C and the iron was removed by filtration and washed with methanol. The filtrate was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous magnesium sulfate filtered and concentrated under reduced pressure to give the title compound as a yellow solid (0.121 g, 66%). (ESI-) m/z 426 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.98 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.69 (m, 1 H) 4.46 (m, 2 H) 5.86 (s, 2 H) 6.96 (m, 2 H) 7.46 (m, 2 H) 8.52 (d, J=6.99 Hz, 1 H) 8.84 (m, 1 H) 13.90 (s, 1 H).

Example 206

({3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}amino)acetonitrile

To the solution of the product from Example 205 (10 mg, 0.023 mmol) in N,N-dimethylformamide (0.2 mL) was added bromoacetonitrile (2.5 μ L, 0.035 mmol) and potassium carbonate (5 mg, 0.035 mmol). The mixture was stirred while heating at 100°C in a microwave reactor for 1 h. After cooling to 25°C, the orange solution was diluted with water and the pH of the aqueous layer was adjusted to pH 5 with acetic acid. The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered, concentrated and purified by flash column chromatography on silica gel eluting with 1% methanol/dichloromethane to give the title compound as a yellow solid (6.0 mg, 55%). MS (ESI-) m/z 465 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.99 (d, J =6.62 Hz, 6 H) 1.58 (m, 2 H) 1.68 (m, 1 H) 4.46 (m, 4 H) 6.92 (m, 1 H) 7.16 (m, 2 H) 7.49 (m, 1 H) 7.61 (d, J =9.19 Hz, 1 H) 8.56 (dd, J =7.90, 1.65 Hz, 1 H) 8.89 (m, 1 H) 14.00 (br s, 1 H) 15.39 (br s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J =6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 4.31 (m, 4 H) 6.49 (t, J =6.62 Hz, 1 H) 6.99 (m, 2 H) 7.13 (m, 2 H) 8.35 (dd, J =7.72, 1.84 Hz, 1 H) 8.51 (dd, J =4.41, 1.84 Hz, 1 H) 15.73 (s, 1 H).

Example 207

7-hydroxy-6-(7-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-(3-methylbutyl)thieno[3,2-*b*]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 125A for the product of Example 1B and substituting the product of Example 183B for the product of Example 1C. The sodium salt was prepared according to the procedure of example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J =6.62 Hz, 6 H) 1.44 (m, 2 H) 1.66 (m, 1 H) 3.81 (s, 3 H) 3.99 (m, 2 H) 7.09 (m, 2 H) 7.16 (m, 2 H) 7.79 (d, J =5.15 Hz, 1 H) 15.87 (s, 1 H). (ESI-) m/z 446 (M-H)⁻.

Example 208

4-benzyl-7-hydroxy-6-(7-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)thieno[3,2-*b*]pyridin-5(4H)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 110B for the product of Example 1B and substituting the product of Example 183B for the product of Example 1C. The sodium salt was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.81 (s, 3

H) 5.26 (s, 2 H) 7.02 (d, J=5.15 Hz, 1 H) 7.11 (m, 1 H) 7.17 (m, 2 H) 7.24 (m, 5 H) 7.71 (d, J=5.15 Hz, 1 H) 15.80 (s, 1 H). (ESI-) m/z 466 (M-H)⁻.

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Example 209A

2-amino-6-methoxy-3-methylbenzenesulfonamide

The title compound was prepared from 3-methoxy-6-methyl-aniline using the
10 procedure described in *JCS Perkin 1*, 1979, 1043.

Example 209B

N-[2-(aminosulfonyl)-3-methoxy-6-methylphenyl]-1-benzyl-4-hydroxy-2-oxo-1,2-dihydro- 1,8-naphthyridine-3-carboxamide

15 The title compound was prepared according to the procedure of Example 84C substituting the product of Example 209A for product of Example 84A to give the title compound (0.22 g, 100%).

Example 209C

1-benzyl-3-(8-methoxy-5-methyl-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8- naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 209B for the product of Example 84C. The solution was then acidified with 6N aqueous HCl (10 mL), filtered and the solid washed with methanol (10
25 mL) to give the title compound as a white solid, (0.12 g, 56% yield). MS (ESI-) m/z 477 (M-H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 2.37 (s, 3 H) 3.83 (s, 3H) 5.52 (s, 2 H) 6.76 (d, J=8.5 Hz, 1 H) 7.16 (m, 2 H) 7.23 (m, 4 H) 7.37 (d, J=8.9 Hz, 1 H) 8.45 (m, 2H), 15.67 (s, 1 H).

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Example 210

1-benzyl-3-(8-hydroxy-5-methyl-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8- naphthyridin-2(1H)-one

A mixture of the product of Example 209C (20 mg, 0.042 mmol) and boron
35 tribromide (1.0M in dichloromethane) (840 μL, 0.84 mmol) in dichloroethane (5 mL) was stirred at 70°C for 16 hrs. The reaction mixture was cooled to 25°C, quenched with water (10 mL) and extracted with ethyl acetate (20 mL). The resulting organic layer was dried over

MgSO₄, filtered, and concentrated under reduced pressure to provide the title compound as a white solid (0.019g, 98% yield). MS (ESI-) m/z 463 (M-H)⁻. The disodium salt of the title compound was prepared according to the procedure of Example 1D using two equivalents of sodium hydroxide. ¹H NMR (300 MHz, DMSO-d₆) δ 2.16 (s, 3 H) 5.52 (s, 2 H) 5.92 (d, J=8.8 Hz, 1 H) 6.79 (d, J=8.8 Hz, 1H) 7.11 (dd, J=7.8,4.8 Hz, 1H) 7.17 (m, 1 H) 7.23 (m, 4 H) 8.42 (m,2H), 14.77 (s, 1 H).

Example 211

{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-5-methyl-1,1-dioxido-4H-1,2,4-benzothiadiazin-8-yl]oxy}acetonitrile

A mixture of the product of Example 210 (23 mg, 0.050 mmol), bromoacetonitrile (14 μL, 0.2 mmol) and potassium carbonate (15 mg, 0.11 mmol) in N,N-dimethylformamide (1 mL) was stirred at 25°C for 3 days. The reaction mixture was concentrated under reduced pressure and the resulting oil was chromatographed on silica gel eluting with ethyl acetate to provide the title compound as a white solid (0.003g, 12% yield). MS (ESI-) m/z 500 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 2.38 (s, 3 H) 5.25 (m, 2H) 5.54 (s, 2 H) 6.93 (m, 1 H) 7.18 (m, 2 H) 7.23 (m, 4 H) 7.37 (m, 1 H) 8.46 (m, 2H).

Example 212 A

2-amino-3-methoxybenzenesulfonamide

The title compound was prepared from 2-methoxyaniline using the procedure as described in *Journal of the Chemical Society, Perkin 1*, **1979**, 1043.

Example 212B

Ethyl (5-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

The title compound was prepared according to the procedure of Example 1C substituting the product of Example 212A for 2-aminobenzenesulfonamide. MS (DCI) m/z 299 (M+H)⁺.

Example 212C

1-Benzyl-4-hydroxy-3-(5-methoxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 1D substituting the product of Example 15A for the product of Example 1B and substituting the product of Example 212B for the product of Example 1C (187 mg, 41 %). The sodium

salt of the title compound was prepared according to the procedure of Example 1D. (ESI-) m/z 461 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.98 (s, 3 H) 5.52 (s, 2 H) 7.18 (m, 9 H) 8.42 (dd, J=7.54, 2.02 Hz, 1 H) 8.47 (dd, J=4.78, 1.84 Hz, 1 H) 15.71 (s, 1 H).

5 Example 213

1-Benzyl-4-hydroxy-3-(5-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 184 substituting the product of Example 212C for the product of Example 183C. (ESI-) m/z 447 (M-H)⁻. The disodium salt of the title compound was prepared according to the procedure of Example 1D using two equivalents of sodium hydroxide. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.53 (s, 2 H) 6.25 (m, 2 H) 6.76 (t, J=7.91 Hz, 1 H) 7.17 (m, 6 H) 8.42 (dd, J=4.78, 1.84 Hz, 1 H) 8.48 (dd, J=7.54, 2.02 Hz, 1 H).

15 Example 214A

{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-5-yl]oxy}acetonitrile

The title compound was prepared according to the procedure as described in Example 185 substituting the product of Example 213 for the product of Example 184. (ESI-) m/z 486 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.51 (s, 2 H) 5.72 (s, 2 H) 7.24 (m, 1 H) 7.28 (s, 1 H) 7.31 (m, 5 H) 7.51 (dd, J=7.91, 4.60 Hz, 1 H) 7.61 (m, 1 H) 8.61 (dd, J=7.72, 1.84 Hz, 1 H) 8.83 (m, 1 H) 14.52 (s, 1 H).

25 Example 214B

3-[5-(2-aminoethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-benzyl-4-hydroxy-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 198 substituting the product of Example 214A for the product of Example 185. (ESI-) m/z 490 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.06 (s, br, 2 H) 4.30 (t, J=4.78 Hz, 2 H) 5.54 (s, 2 H) 5.72 (s, br, 2 H) 7.20 (m, 9 H) 8.50 (dd, J=4.78, 1.84 Hz, 1 H) 8.69 (dd, J=7.72, 2.21 Hz, 1 H) 16.05 (s, 1 H).

35 Example 215

2-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-

benzothiadiazin-5-ylloxy}acetamide

The title compound was prepared according to the procedure as described in Example 190 substituting the product of Example 213 for the product of Example 184.

(ESI-) m/z 504 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.64 (s, 2 H) 5.53 (s, 2 H) 7.22 (m, 9 H) 7.88 (s, 1 H) 8.13 (s, 1 H) 8.46 (dd, $J=7.72$, 1.84 Hz, 1 H) 8.51 (dd, $J=4.78$, 1.84 Hz, 1 H) 16.15 (s, 1 H).

Example 216

1-benzyl-4-hydroxy-3-{5-[(4-nitrobenzyl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 185 substituting the product of Example 213 for the product of Example 184 and substituting para-nitrobenzyl bromide for 2-bromoacetonitrile. (ESI-) m/z 582 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.54 (s, 2 H) 5.55 (s, 2 H) 7.26 (m, 9 H) 8.08 (s, 1 H) 8.11 (s, 1 H) 8.28 (s, 1 H) 8.31 (s, 1 H) 8.48 (q, $J=2.08$ Hz, 1 H) 8.50 (s, 1 H) 16.01 (s, 1 H).

Example 217A

N-[2-(aminosulfonyl)phenyl]-1-benzyl-6-chloro-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxamide

The title compound was prepared according to the procedure of Example 84C substituting ethyl 1-benzyl-6-chloro-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate for the product of Example 84B and substituting 2-amino-benzenesulfonamide for the product of Example 84A. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.64 (s, 2 H) 7.25 (m, 5 H) 7.44 (t, $J=7.72$ Hz, 1 H) 7.52 (s, 2 H) 7.67 (m, 1 H) 7.93 (m, 2 H) 8.56 (d, $J=2.57$ Hz, 1 H) 8.87 (d, $J=2.57$ Hz, 1 H) 12.34 (s, 1 H) 16.76 (s, 1 H).

Example 217B

1-Benzyl-6-chloro-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 217A for the product of Example 84C. The sodium salt of the title compound was prepared according to the procedure as described in Example 1D. MS (DCI/NH₃) m/z 465 (M+H)⁺, 483 (M+NH₃)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.49 (s, 2 H) 7.17 (m, 6 H) 7.48 (t, $J=7.35$ Hz, 1 H) 7.83 (dd, $J=7.72$, 1.47 Hz, 1 H) 8.32 (d,

$J=2.57$ Hz, 1 H) 8.46 (m, 2 H) 11.20 (s; 1 H).

Example 218A

5 *N*-[2-(aminosulfonyl)phenyl]-1-benzyl-4-hydroxy-2-oxo-6-phenyl-1,2-dihydro-1,8-naphthyridine-3-carboxamide

The title compound was prepared according to the procedure of Example 84C substituting ethyl 1-benzyl-6-phenyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate for the product of Example 84B and substituting 2-amino-benzenesulfonamide
10 for the product of Example 84A. ^1H NMR (300 MHz, DMSO- d_6) δ ppm 5.72 (s, 2 H) 7.28 (m, 6 H) 7.44 (m, 2 H) 7.54 (m, 3 H) 7.67 (m, 1 H) 7.85 (d, $J=6.99$ Hz, 2 H) 7.92 (dd, $J=8.09$, 1.47 Hz, 1 H) 7.99 (d, $J=8.09$ Hz, 1 H) 8.70 (d, $J=2.21$ Hz, 1 H) 9.17 (d, $J=2.21$ Hz, 1 H) 12.41 (s, 1 H) 16.80 (s, 1 H).

Example 218B

15 1-benzyl-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-phenyl-1,8-naphthyridin-2(1*H*)-one

The title compound was prepared according to the procedure of Example 84D substituting the product of Example 218A for the product of Example 84C. MS (ESI-) m/z
20 507 (M-H) $^-$. The sodium salt of the title compound was prepared to the procedure as described in Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ ppm 5.53 (s, 2 H) 7.04 (m, 2 H) 7.26 (m, 7 H) 7.48 (t, $J=7.54$ Hz, 2 H) 7.58 (d, $J=8.09$ Hz, 1 H) 7.70 (d, $J=7.35$ Hz, 2 H) 8.51 (d, $J=2.21$ Hz, 1 H) 8.65 (d, $J=2.57$ Hz, 1 H)

Example 219A

2-amino-4-methoxybenzenesulfonamide

The title compound was prepared according to the procedure as described in Topliss et al, J. Med. Chem. 6, **1963**, 122.

Example 219B

Ethyl (6-methoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)acetate

The title compound was prepared according to the procedure of Example 1C substituting the product of Example 219A for 2-aminobenzenesulfonamide. MS (DCI) m/z
35 299 (M+H) $^+$.

Example 219C

1-benzyl-4-hydroxy-3-(6-methoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1*H*)-one

The title compound was prepared according to the procedure as described in Example 1D substituting the product of Example 15A for the product of Example 1B and substituting the product of Example 219B for the product of Example 1C. The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) *m/z* 461 (M-H). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.90 (m, 3 H) 5.72 (s, 2 H) 7.08 (dd, *J*=8.82, 2.21 Hz, 1 H) 7.26 (m, 6 H) 7.51 (dd, *J*=8.09, 4.78 Hz, 1 H) 7.82 (d, *J*=9.19 Hz, 1 H) 8.61 (dd, *J*=8.09, 1.84 Hz, 1 H) 8.83 (dd, *J*=4.60, 2.02 Hz, 1 H) 13.97 (s, 1 H).

Example 220A

N-[3-amino-4-(aminosulfonyl)phenyl]acetamide

The title compound was prepared according to the procedure as described in Topliss et al, J. Med. Chem. 6, 1963, 122.

Example 220B

Ethyl [6-(acetylamino)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl]acetate

The title compound was prepared according to the procedure as described in Example 1C substituting the product of Example 220A for 2-aminobenzenesulfonamide. MS(DCI) *m/z* 326 (M+H)⁺.

Example 220C

N-[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-6-yl]acetamide

The title compound was prepared according to the procedure as described in Example 1D substituting the product of Example 15A for the product of Example 1B and substituting the product of Example 220B for the product of Example 1C. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 6.82 (d, *J*=1.84 Hz, 2 H) 6.95 (dd, *J*=8.64, 2.02 Hz, 2 H) 7.29 (d, *J*=4.04 Hz, 1 H) 7.44 (dd, *J*=8.09, 4.78 Hz, 2 H) 7.74 (m, 2 H) 8.47 (m, 1 H) 8.78 (m, 1 H) 10.81 (s, 1 H) 12.86 (s, 1 H) 14.06 (s, 1 H). MS (ESI-) *m/z* 447 (M-H).

Example 221

1-benzyl-4-hydroxy-3-(6-hydroxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1,8-

naphthyridin-2(1H)-one

A mixture of the product of Example 219C (20 mg, 0.043 mmole) and boron tribromide (1.0 M in dichloromethane, 20 equivalents) in 1,2 dichloroethane (5 mL) was stirred at reflux for 28 hours. The reaction mixture was cooled to 25°C, diluted with tetrahydrofuran and aqueous 1N HCl, and refluxed for 2 hours. The resulting solid was collected by filtration and dried to give the title compound (11.3 mg). The disodium salt of the title compound was prepared according to the procedure of Example 1D using two equivalents of sodium hydroxide. MS (ESI-) m/z 447 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 6.82 (d, J=1.84 Hz, 2 H) 6.95 (dd, J=8.64, 2.02 Hz, 2 H) 7.29 (d, J=4.04 Hz, 1 H) 7.44 (dd, J=8.09, 4.78 Hz, 2 H) 7.74 (m, 2 H) 8.47 (m, 1 H) 8.78 (m, 1 H) 10.81 (s, 1 H) 12.86 (s, 1 H) 14.06 (s, 1 H).

Example 222A2-amino-6-methylbenzenesulfonamide

The title compound was prepared according to the procedure as described in Topliss et al, J. Med. Chem. 6, 1963, 122.

Example 222BEthyl (8-methyl-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

The title compound was prepared according to the procedure of Example 1C substituting the product of Example 222A for 2-aminobenzenesulfonamide.

Example 222C1-benzyl-4-hydroxy-3-(8-methyl-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 1D substituting the product of Example 15A for the product of Example 1B and substituting the product of Example 222B for the product of Example 1C. (35.8 mg, 10 %). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) m/z 446 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.56 (s, 3 H) 5.52 (s, 2 H) 7.06 (dd, J=7.72, 3.31 Hz, 2 H) 7.13 (m, 2 H) 7.23 (m, 4 H) 7.41 (t, J=7.72 Hz, 2 H) 8.39 (d, J=1.84 Hz, 1 H) 8.48 (dd, J=4.60, 2.02 Hz, 1 H) 15.70 (s, 1 H).

Example 223

4-hydroxy-3-(5-methoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 12A for the product of Example 1B and substituting the product of Example 212B for the product of Example 1C. The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) *m/z* 441 (M-H)⁻. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.95 (s, 3 H) 0.98 (s, 3 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 3.98 (s, 3 H) 4.29 (t, *J* = 7.50 Hz, 2 H) 7.11 (dd, *J* = 7.72, 4.78 Hz, 1 H) 7.23 (m, 3 H) 8.38 (dd, *J* = 7.35, 1.84 Hz, 1 H) 8.51 (dd, *J* = 4.41, 1.84 Hz, 1 H) 15.80 (s, 1 H).

Example 224

7-hydroxy-6-(5-methoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-(3-methylbutyl)thieno[3,2-*b*]pyridin-5(4*H*)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 125A for the product of Example 1B and substituting the product of Example 212B for the product of Example 1C. The sodium salt of the title compound was prepared according to the procedure as described in Example 1D. (ESI-) *m/z* 446 (M-H)⁻. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.95 (s, 3 H) 0.97 (s, 3 H) 1.44 (m, 2 H) 1.67 (m, 1 H) 3.99 (m, 5 H) 7.08 (d, *J* = 5.52 Hz, 1 H) 7.19 (m, 3 H) 7.79 (d, *J* = 5.15 Hz, 1 H) 15.75 (s, 1 H).

Example 225

4-Benzyl-7-hydroxy-6-(5-methoxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)thieno[3,2-*b*]pyridin-5(4*H*)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 110B for the product of Example 1B and substituting the product of Example 212B for the product of Example 1C. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.97 (s, 3 H) 5.26 (s, 2 H) 7.01 (d, *J* = 5.52 Hz, 1 H) 7.25 (m, 8 H) 7.70 (d, *J* = 5.52 Hz, 1 H) 15.69 (s, 1 H). MS (ESI-) *m/z* 466 (M-H)⁻.

Example 226A

methyl 2-[2-benzylidenehydrazino]benzoate

2-(*N*²-Benzylidene-hydrazino)-benzoic acid (5.0 g, 20.81 mmol) in 1:1 tetrahydrofuran and methanol (50 mL) was reacted with a solution of trimethylsilyl

diazomethane in hexanes (2.0M, 12 mL, 25.0 mmol) at 0°C for 1 hour then stirred at 25°C for 48 hours. The solvent was removed under vacuum to give the title compound as a solid (6.00 g, 100%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.87 (s, 3 H) 6.84 (td, J=7.54, 1.10 Hz, 1 H) 7.41 (m, 3 H) 7.54 (m, 1 H) 7.74 (m, 3 H) 7.86 (dd, J=8.09, 1.47 Hz, 1 H) 8.21 (s, 1 H) 11.02 (s, 1 H).

Example 226B

methyl 2-[2-benzylidene-1-(3-ethoxy-3-oxopropanoyl)hydrazino]benzoate

The product of Example 226A (5.29 g, 20.81 mmol) in toluene (80 mL) was reacted with ethyl chloromalonate (2.68 mL, 25.0 mmol) at reflux for 4 hours. The reaction mixture was cooled to 25°C and concentrated under vacuum. The residue was triturated with diethyl ether and hexanes (3:1) to give the title compound (5.17 g, 70%). MS (DCI) m/z 355 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.32 (s, 2 H) 3.69 (s, 3 H) 3.73 (s, 3 H) 7.16 (s, 1 H) 7.32 (dd, J=7.72, 1.10 Hz, 1 H) 7.40 (m, 3 H) 7.63 (m, 2 H) 7.70 (td, J=7.63, 1.29 Hz, 1 H) 7.85 (td, J=7.72, 1.47 Hz, 1 H) 8.10 (dd, J=7.72, 1.47 Hz, 1 H).

Example 226C

Ethyl 4-hydroxy-2-oxo-1-[[phenylmethylene]amino]-1,2-dihydroquinoline-3-carboxylate

The product of Example 226B (5.17 g, 14.59 mmol) in ethanol (100 mL) was reacted with sodium ethoxide (21% by weight in ethanol, 5.50 mL, 14.60 mmol) at 25°C then heated at 50°C for 1 hour. After cooling to 25°C, the reaction mixture was poured into water, acidified to pH 4 with 1M hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under vacuum to give the title compound (4.51 g, 96%). MS (DCI) m/z 323 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.73 (s, 3 H) 7.21 (m, 1 H) 7.56 (m, 5 H) 7.95 (m, 2 H) 8.03 (d, J=7.72 Hz, 1 H) 9.08 (s, 1 H).

767087 Example 226D PKD

1-amino-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226C (4.51 g, 14.00 mmol) was reacted with 2-amino benzenesulfonamide (2.41 g, 14.00 mmol) in toluene (65 mL) at reflux for 6 hours. After cooling to 25°C, the solid (5.52 g) was collected by filtration and reacted further with aqueous 10% potassium hydroxide (100 mL) for 8 hours at 130°C. After cooling to 25°C, the reaction was poured into ice and acidified to pH 2 with 1M hydrochloric acid. The resulting solid was isolated by filtration and dried to give the title compound (3.50 g, 71%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 5.31 (s, 2 H) 7.05 (t, J=8.09 Hz, 1 H) 7.27 (m, 2 H)

7.53 (m, 2 H) 7.67 (m, 2 H) 8.07 (dd, $J=8.09$, 1.47 Hz, 1 H) 16.38 (s, 1 H).

5

Example 227A

3-(1,1-Dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1-propylbutylidene)amino]quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 4-heptanone (0.63 mL, 4.49 mmol) in N,N-dimethylacetamide (1 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound as a solid (0.032 g, 32%). MS (ESI-) m/z 453 (M-H)⁻.

15

Example 227B

1-(1-propyl-butylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 227A (0.032 g, 0.07 mmol) in tetrahydrofuran (2 mL) and methanol (0.010 mL, 0.14 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.055 mL, 0.11 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was suspended in tetrahydrofuran (2 mL) and adsorbed onto approximately 0.5g of silica gel and evaporated. A slurry of the crude product and silica in dichloromethane was loaded onto a 2 g Alltech Sep-pack and eluted with dichloromethane. Product containing fractions were combined and concentrated under vacuum to give the title compound (0.013 g, 40%). MS (ESI-) m/z 453 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.85 (m, 6 H) 1.33 (m, 8 H) 3.13 (m, 1 H) 5.66 (d, $J=4.04$ Hz, 1 H) 7.05 (m, 1 H) 7.28 (m, 2 H) 7.51 (m, 2 H) 7.68 (m, 2 H) 8.06 (dd, $J=7.72$, 1.47 Hz, 1 H) 16.32 (s, 1 H).

35

Example 228A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(2-methylpropylidene)amino]quinolin-2(1H)-one

The product of Example 226D (0.178 g, 0.50 mmol) was reacted with 2-

methylpropanal (0.9 mL, 10.0 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 228B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

The product of Example 228A (0.132 g, 0.32 mmol) in tetrahydrofuran (6 mL) and methanol (0.026 mL, 0.64 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.24 mL, 0.48 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (12 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with 1:1 ethyl acetate:hexane (10 mL) and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.03 (d, J=6.62 Hz, 6 H) 1.86 (m, 1 H) 2.73 (m, 2 H) 5.94 (t, J=7.35 Hz, 1 H) 7.07 (t, J=7.35 Hz, 1 H) 7.27 (m, 2 H) 7.54 (m, 2 H) 7.60 (d, J=6.99 Hz, 1 H) 7.66 (d, J=6.99 Hz, 1 H) 8.08 (d, J=8.09 Hz, 1 H) 16.27 (s, 1 H). MS (ESI-) (M-H)⁻ m/z 411.

Example 229A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(1-ethylpropylidene)amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.178 g, 0.5 mmol) was reacted with pentan-3-one (0.53 mL, 5.0 mmol) in N,N-dimethylacetamide (4 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 229B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(1-ethylpropyl)amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 229A (0.122 g, 0.287 mmol) in tetrahydrofuran (8 mL) and methanol (0.023 mL, 0.57 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.215 mL, 0.43 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4,

diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.83 (s, 3 H) 0.98 (s, 3 H) 1.31 (m, 2 H) 1.48 (m, 2 H) 2.99 (m, 1 H) 5.70 (d, J=4.04 Hz, 1 H) 7.05 (t, J=7.17 Hz, 1 H) 7.28 (m, 2 H) 7.51 (m, 2 H) 7.66 (d, J=8.09 Hz, 1 H) 7.72 (d, J=8.09 Hz, 1 H) 8.06 (d, J=7.72 Hz, 1 H) 16.32 (s, 1 H). MS (ESI-) (M-H)⁻ m/z 425.

Example 230A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[pentylideneamino]quinolin-2(1H)-one

The product of Example 226D (0.05 g, 0.14 mmol) was reacted with pentanal (0.015 mL, 1.4 mmol) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 230B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(pentylamino)quinolin-2(1H)-one

The product of Example 230A (0.034 g, 0.08 mmol) in tetrahydrofuran (2 mL) and methanol (0.0064 mL, 0.16 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.06 mL, 0.12 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.90 (t, J=6.99 Hz, 3 H) 1.37 (m, 4 H) 1.55 (m, 2 H) 2.73 (m, 2 H) 5.90 (t, J=6.80 Hz, 1 H) 7.07 (t, J=7.72 Hz, 1 H) 7.26 (m, 2 H) 7.52 (m, 2 H) 7.60 (d, J=8.09 Hz, 1 H) 7.66 (d, J=8.09 Hz, 1 H) 8.09 (d, J=8.09 Hz, 1 H) 16.27 (s, 1 H). MS (ESI-) (M-H)⁻ m/z 425.

Example 231A

1-(cyclohexylideneamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-

hydroxyquinolin-2(1H)-one

The product of Example 226D (0.155 g, 0.60 mmol) was reacted with cyclohexanone (20 mole equivalents) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated.

5 The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 231B1-(cyclohexylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

10 The product of Example 231A (0.087 g, 0.2 mmol) in tetrahydrofuran (4 mL) and methanol (0.016 mL, 0.4 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.15 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5 mL), and the resulting precipitate was collected by filtration and dried to give
15 the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.13 (m, 6 H) 1.58 (m, 2 H) 1.75 (m, 2 H) 2.97 (m, 1 H) 5.68 (d, J=3.68 Hz, 1 H) 7.05 (t, J=7.54 Hz, 1 H) 7.27 (d, J=8.09 Hz, 1 H) 7.30 (d, J=8.09 Hz, 1 H) 7.49 (t, J=7.72 Hz, 1 H) 7.55 (t, J=7.72 Hz, 1 H) 7.67 (d, J=8.09 Hz, 1 H) 7.76 (d, J=8.46 Hz, 1 H) 8.06 (d, J=7.72 Hz, 1 H) 16.30 (s, 1 H).
20 MS (ESI-) (M-H)⁻ m/z 437.

Example 232A

25 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-{[(2-methyl-1,3-thiazol-4-yl)methylene]amino}quinolin-2(1H)-one

The product of Example 226D (0.119 g, 0.33 mmol) was reacted with 2-methyl-1,3-thiazole-4-carbaldehyde (5 mol equivalents) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction mixture was cooled to
30 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 232B

35 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-{[(2-methyl-1,3-thiazol-4-yl)methyl]amino}quinolin-2(1H)-one

The product of Example 232A (0.097 g, 0.208 mmol) in tetrahydrofuran (5 mL) and methanol (0.016 mL, 0.40 mmol) at 0°C was treated with dropwise addition of a 2.0M

solution of lithium borohydride in tetrahydrofuran (0.15 mL, 0.3 mmol). The reaction was stirred at 25°C for 3 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on C-18 reverse phase column eluting with
5 water:acetonitrile 90:10 - 0:100 to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.68 (s, 3 H) 3.24 (m, 2 H) 6.33 (m, 1 H) 7.10 (m, 1 H) 7.31 (m, 2 H) 7.43 (s, 1 H) 7.61 (m, 4 H) 8.08 (d, J=7.72 Hz, 1 H) 16.24 (s, 1 H). MS (ESI-) (M-H)⁻ m/z 466.

Example 233A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1-methylethylidene)amino]quinolin-2(1H)-one

15 The product of Example 226D (0.080 g, 0.22 mmol) was reacted with acetone (0.34 mL, 4.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 125°C for 25 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 233B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isopropylamino)quinolin-2(1H)-one

20 The product of Example 233A (0.044 g, 0.11 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.28 mmol) at 0°C was treated with dropwise addition of a 2.0M
25 solution of lithium borohydride in tetrahydrofuran 0.085mL, 0.17 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure
30 of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.99 (m, 6 H) 3.94 (m, 1 H) 5.65 (d, J=4.41 Hz, 1 H) 7.04 (t, J=7.35 Hz, 1 H) 7.28 (m, 2 H) 7.51 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.75 (d, J=8.46 Hz, 1 H) 8.06 (dd, J=8.09, 1.47 Hz, 1 H) 16.28 (s, 1 H). (ESI-) m/z 397 (M-H).

Example 234A

1-(cyclobutylideneamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with cyclobutanone (0.50 mL, 7.10 mmol) in N,N-dimethylacetamide (0.50 mL) in a sealed tube at 125°C for 40 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 234B

1-(cyclobutylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 234A (0.032 g, 0.078 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.28 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.025 mL, 0.050 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.54 (m, 1 H) 1.98 (m, 4 H) 3.61 (m, 2 H) 6.09 (d, J=6.25 Hz, 1 H) 7.06 (td, J=7.35, 1.10 Hz, 1 H) 7.27 (m, 2 H) 7.53 (m, 2 H) 7.65 (m, 2 H) 8.06 (dd, J=7.91, 1.65 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 409 (M-H)⁻.

Example 235A

1-(cyclopentylideneamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.079 g, 0.22 mmol) was reacted with cyclopentanone (0.195 mL, 2.22 mmol) in N,N-dimethylacetamide (1.50 mL) in a sealed tube at 130°C for 30 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 235B

1-(cyclopentylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 235A (0.030 g, 0.071 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.28 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.060 mL, 0.12 mmol). The reaction was

stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.61 (m, 8 H) 3.70 (m, 1 H) 5.68 (d, J=4.41 Hz, 1 H) 7.05 (t, J=7.35 Hz, 1 H) 7.28 (t, J=8.27 Hz, 2 H) 7.54 (m, 2 H) 7.69 (dd, J=15.81, 8.09 Hz, 2 H) 8.06 (dd, J=8.09, 1.47 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 423 (M-H)⁻.

Example 236A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-methylcyclopentylidene]amino)quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 3-methylcyclopentanone (0.50 mL, 5.09 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 40 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 236B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-methylcyclopentyl]amino)quinolin-2(1H)-one

The product of Example 236A (0.068 g, 0.16 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.28 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.100 mL, 0.20 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.03 (m, 3 H) 1.35 (m, 1 H) 1.78 (m, 4 H) 2.56 (m, J=5.52 Hz, 2 H) 3.69 (m, 1 H) 5.78 (m, 1 H) 7.05 (m, 1 H) 7.27 (m, 2 H) 7.52 (m, 2 H) 7.69 (m, 2 H) 8.06 (dd, J=7.72, 1.47 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 437 (M-H)⁻.

Example 237A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-4H-pyran-4-ylideneamino)quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with tetrahydro-4H-

pyran-4-one (0.215 mL, 2.33 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 130°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

5

Example 237B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-2H-pyran-4-ylamino)quinolin-2(1H)-one

The product of Example 237A (0.082g, 0.19 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.140 mL, 0.28 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and , and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.86 (m, 1 H) 1.24 (m, 2 H) 1.48 (m, 2 H) 3.20 (m, J=18.02, 10.66 Hz, 2 H) 3.81 (m, 2 H) 5.82 (d, J=4.04 Hz, 1 H) 7.04 (m, J=7.72 Hz, 1 H) 7.27 (m, J=8.46, 8.46 Hz, 2 H) 7.52 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.76 (d, J=8.09 Hz, 1 H) 8.04 (d, J=1.47 Hz, 1 H). MS (ESI-) m/z 439 (M-H)⁻.

20

Example 238A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-([1-ethylbutylidene]amino)-4-hydroxyquinolin-2(1H)-one

25

The product of Example 226D (0.085 g, 0.24 mmol) was reacted with hexan-3-one (0.55 mL, 4.48 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 140°C for 60 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

30

Example 238B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-([1-ethylbutyl]amino)-4-hydroxyquinolin-2(1H)-one

35

The product of Example 238A (0.049 g, 0.11 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.152 mL, 0.30 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4,

diluted with water, and the resulting precipitate was collected by filtration and dried to give the title compound. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm
5 0.88 (m, 6 H) 1.37 (m, 6 H) 3.05 (m, 1 H) 5.68 (m, 1 H) 7.05 (m, 1 H) 7.28 (m, 2 H) 7.52 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.71 (m, 1 H) 8.06 (dd, J=7.72, 1.47 Hz, 1 H) 16.32 (s, 1 H). MS (ESI-) m/z 439 (M-H)⁺.

Example 239A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([(3R)-3-methylcyclohexylidene]amino)quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with (3R)-3-methylcyclohexanone 0.275 mL, 2.25 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 130°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 239B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([(3R)-3-methylcyclohexyl]amino)quinolin-2(1H)-one

The product of Example 239A (0.045 g, 0.10 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.28 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.075 mL, 0.15 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried to give the title compound. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm
25 0.83 (m, 3 H) 1.22 (m, 3 H) 1.73 (m, 3 H) 2.99 (m, 1 H) 5.67 (d, J=4.04 Hz, 1 H) 7.04 (t, J=6.99 Hz, 1 H) 7.28 (t, J=8.27 Hz, 2 H) 7.53 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.74 (d, J=8.09 Hz, 1 H) 8.06 (m, 1 H). MS (ESI-) m/z 451 (M-H)⁺.

Example 240A2-(2-cycloheptylidenehydrazino)benzoic acid

The title compound was prepared according to the procedure as described in Example 162A, substituting cycloheptanone for benzaldehyde.

Example 240B1-(cycloheptylideneamino)-2H-3,1-benzoxazine-2,4(1H)-dione

The title compound was prepared according to the procedure as described in Example 162B, substituting the product of Example 240A for the product of Example 162A.

Example 240C1-(cycloheptylideneamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 1D, substituting the product of Example 240B for the product of Example 1B.

Example 240D1-(cycloheptylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 240C (0.099 g, 0.22 mmol) in tetrahydrofuran (4.0 mL) (0.099 g, 0.22 mmol) in tetrahydrofuran (4.0 mL) and methanol (0.020 mL, 0.49 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.16 mL, 0.32 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.43 (m, 11 H) 1.87 (m, 1 H) 3.25 (m, 1 H) 5.53 (d, J=3.68 Hz, 1 H) 7.04 (m, 1 H) 7.28 (m, 2 H) 7.51 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.73 (d, J=8.46 Hz, 1 H) 8.05 (dd, J=7.72, 1.47 Hz, 1 H) 16.30 (s, 1 H). MS (ESI-) m/z 451 (M-H)⁻.

Example 241A3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-{[3-ethylcyclopentylidene]amino}-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 3-ethylcyclopentanone (0.380 mL, 3.30 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed

tube at 135°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 241B

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-{[3-ethylcyclopentyl]amino}-4-hydroxyquinolin-2(1*H*)-one

The product of Example 241A (0.031 g, 0.068 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.25 mmol) at 0 °C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.055 mL, 0.11 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.85 (m, 3 H) 1.56 (m, 8 H) 3.65 (m, 2 H) 5.75 (m, 1 H) 7.05 (t, J=6.99 Hz, 1 H) 7.28 (m, 2 H) 7.52 (m, 2 H) 7.69 (m, 2 H) 8.06 (dd, J=7.90, 1.65 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 451 (M-H)⁻.

Example 242A

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[[1-isopropylbutylidene]amino]quinolin-2(1*H*)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 2-methylhexan-3-one (0.620 mL, 4.48 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135 °C for 60 min then at 145 °C for 60 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 242B

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1-isopropylbutyl]amino}quinolin-2(1*H*)-one

The product of Example 242A (0.049 g, 0.11 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.25 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.085 mL, 0.17 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The

crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.68 (m, 1 H) 1.18 (m, 9 H) 2.49 (m, 4 H) 3.00 (m, J=44.49 Hz, 1 H) 5.73 (d, J=20.22 Hz, 1 H) 7.04 (m, 1 H) 7.27 (m, 2 H) 7.52 (m, 2 H) 7.71 (m, 2 H) 8.06 (dd, J=8.09, 1.47 Hz, 1 H) 16.33 (s, 1 H). MS (ESI-) m/z 453 (M-H)⁻.

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Example 243A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-phenylethylidene]amino)quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 1-phenylethanone (0.49 mL, 4.20 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 40 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

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Example 243B

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3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-phenylethyl]amino)quinolin-2(1H)-one

The product of Example 243A (0.093 g, 0.20 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.152 mL, 0.30 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.31 (m, 3 H) 4.41 (d, J=68.76 Hz, 1 H) 5.85 (m, 1 H) 7.28 (m, J=7.54, 7.54 Hz, 7 H) 7.59 (m, 4 H) 8.07 (m, 2 H) 16.30 (s, 1 H). MS (ESI-) m/z 459 (M-H)⁻.

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Example 244A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-thien-3-ylethylidene]amino)quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 1-thien-3-ylethanone (0.14 g, 1.11 mmol) in N,N-dimethylacetamide (0.50 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 244B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[[1-thien-3-ylethyl]amino]quinolin-2(1H)-one

The product of Example 244A (0.070 g, 0.15 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.090 mL, 0.18 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.26 (m, 3 H) 4.58 (m, 1 H) 5.74 (s, 1 H) 7.07 (m, 1 H) 7.18 (m, 1 H) 7.28 (m, 3 H) 7.37 (s, 1 H) 7.55 (m, 2 H) 7.66 (m, 1 H) 7.96 (d, J=6.62 Hz, 1 H) 8.07 (s, 1 H) 16.30 (s, 1 H). MS (ESI-) m/z 465 (M-H)⁻.

Example 245A

1-[[3,5-dimethylcyclohexylidene]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 3,5-dimethylcyclohexanone (0.57 g, 4.52 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 40 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 245B

1-[[3,5-dimethylcyclohexyl]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 245A (0.064 g, 0.14 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.25 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.100 mL, 0.20 mmol). The reaction was

stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.55 (m, 2 H) 0.87 (m, 6 H) 1.67 (m, 6 H) 3.05 (m, 1 H) 5.66 (dd, J=5.70, 3.86 Hz, 1 H) 7.05 (m, 1 H) 7.28 (t, J=8.27 Hz, 2 H) 7.51 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 7.73 (t, J=7.54 Hz, 1 H) 8.06 (dd, J=7.91, 1.29 Hz, 1 H). MS (ESI-) m/z 465 (M-H)⁻.

Example 246A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-isopropylcyclohexylidene)amino]quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 4-isopropylcyclohexanone (0.63 mL, 4.11 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 246B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-isopropylcyclohexyl)amino]quinolin-2(1H)-one

The product of Example 246A (0.095 g, 0.20 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.30 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.86 (m, 6 H) 1.43 (m, 7 H) 1.87 (m, 1 H) 2.94 (m, 1 H) 3.14 (m, 1 H) 5.71 (m, 1 H) 7.04 (t, J=7.54 Hz, 1 H) 7.28 (t, J=8.46 Hz, 2 H) 7.50 (m, 2 H) 7.70 (m, 2 H) 8.06 (m, 1 H) 16.30 (s, 1 H). MS (ESI-) m/z 479 (M-H)⁻.

Example 247A

1-[3,4-dihydronaphthalen-2(1H)-ylideneamino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-

yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 3,4-dihydronaphthalen-2(1H)-one (0.60 mL, 4.54 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 247B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[1,2,3,4-tetrahydronaphthalen-2-ylamino]quinolin-2(1H)-one

The product of Example 247A (0.070 g, 0.14 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.010 mL, 0.25 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.110 mL, 0.22 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.73 (s, 2 H) 3.27 (d, J=12.50 Hz, 4 H) 5.93 (d, J=3.68 Hz, 1 H) 7.07 (m, 6 H) 7.28 (t, J=7.54 Hz, 3 H) 7.55 (m, 2 H) 7.66 (d, J=7.72 Hz, 1 H) 8.07 (dd, J=7.72, 1.47 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 485 (M-H)⁻.

Example 248A3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-{[3-(trifluoromethyl)cyclohexylidene]amino}quinolin-2(1H)-one

The product of Example 226D (0.080 g, 0.22 mmol) was reacted with 3-(trifluoromethyl)cyclohexanone (0.75 mL, 4.54 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 40 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with diethyl ether and filtered to give the title compound.

Example 248B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-{[3-(trifluoromethyl)cyclohexyl]amino}quinolin-2(1H)-one

The product of Example 248A (0.103 g, 0.20 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.015 mL, 0.42 mmol) at 0°C was treated with dropwise addition of a 2.0M

solution of lithium borohydride in tetrahydrofuran (0.15 mL, 0.30 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water, and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.21 (m, 4 H) 1.76 (m, 2 H) 2.31 (m, 1 H) 3.11 (m, 2 H) 3.97 (m, 1 H) 5.81 (d, J=19.85 Hz, 1 H) 7.05 (m, 1 H) 7.28 (m, 2 H) 7.53 (m, 2 H) 7.66 (d, J=8.09 Hz, 1 H) 7.75 (d, J=7.72 Hz, 1 H) 8.06 (dd, J=8.09, 1.47 Hz, 1 H). MS (ESI-) m/z 505 (M-H)⁻.

Example 249A

1-[butylideneamino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with butyraldehyde (0.135 mL, 1.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 249B

1-(butylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 249A (0.040 g, 0.097 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.194 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.074 mL, 0.148 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and washed with water (2x5.0 mL) and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.93 (t, J=7.17 Hz, 3 H) 1.48 (m, 4 H) 2.77 (m, 2 H) 5.90 (t, J=6.99 Hz, 1 H) 7.07 (m, 1 H) 7.27 (m, 2 H) 7.58 (m, 3 H) 7.66 (d, J=8.09 Hz, 1 H) 8.08 (dd, J=8.09, 1.47 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) m/z 411 (M-H)⁻.

Example 250A

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-methylbutylidene]amino)quinolin-2(1*H*)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 3-methylbutanal (0.161 mL, 1.50 mmol) in *N,N*-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 250B

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylbutyl)amino]quinolin-2(1*H*)-one

The product of Example 250A (0.041 g, 0.097 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.194 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.074 mL, 0.148 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.92 (s, 3 H) 0.94 (s, 3 H) 1.45 (q, J=7.11 Hz, 2 H) 1.73 (m, 1 H) 2.79 (m, 2 H) 5.87 (t, J=6.80 Hz, 1 H) 7.07 (t, J=7.35 Hz, 1 H) 7.28 (t, J=8.46 Hz, 2 H) 7.55 (m, 3 H) 7.66 (d, J=7.72 Hz, 1 H) 8.08 (dd, J=7.91, 1.29 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) *m/z* 425 (M-H)⁻.

Example 251A

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-([3-furylmethylene]amino)-4-hydroxyquinolin-2(1*H*)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 3-furaldehyde (0.147 mL, 1.78 mmol) in *N,N*-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 251B

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-[(3-furylmethyl)amino]-4-hydroxyquinolin-2(1*H*)-one

The product of Example 251A (0.028 g, 0.064 mmol) in tetrahydrofuran (1.3 mL) and

methanol (0.005 mL, 0.128 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.050 mL, 0.100 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (6.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.79 (m, 2 H) 6.03 (t, J=6.80 Hz, 1 H) 6.65 (s, 1 H) 7.08 (t, J=7.35 Hz, 1 H) 7.27 (m, 3 H) 7.54 (m, 2 H) 7.68 (m, 3 H) 8.08 (d, J=7.72 Hz, 1 H) 16.26 (s, 1 H). MS (ESI-) m/z 435 (M-H)⁺.

Example 252A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-{[2-furylmethylene]amino}-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 2-furaldehyde (0.147 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 252B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(2-furylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 252A (0.058 g, 0.134 mmol) in tetrahydrofuran (3.0 mL) and methanol (0.010 mL, 0.268 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.105 mL, 0.210 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (6.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.03 (s, 2 H) 6.20 (t, J=6.07 Hz, 1 H) 6.35 (m, 1 H) 7.05 (t, J=7.72 Hz, 1 H) 7.29 (t, J=7.72 Hz, 3 H) 7.46 (t, J=7.72 Hz, 1 H) 7.56 (m, 2 H) 7.67 (d, J=7.72 Hz, 2 H) 8.06 (d, J=8.09 Hz, 1 H) 16.24 (s, 1 H). MS (ESI-) m/z 435 (M-H)⁺.

Example 253A3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(thien-2-ylmethylene)amino]quinolin-2(1H)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with thiophene-2-carbaldehyde (0.166 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 253B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(thien-2-ylmethyl)amino]quinolin-2(1H)-one

The product of Example 253A (0.025 g, 0.055 mmol) in tetrahydrofuran (1.2 mL) and methanol (0.005 mL, 0.110 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.044 mL, 0.088 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.18 (s, 2 H) 6.16 (t, J=6.62 Hz, 1 H) 7.01 (dd, J=5.15, 3.31 Hz, 1 H) 7.07 (d, J=7.72 Hz, 1 H) 7.12 (m, 1 H) 7.29 (t, J=7.54 Hz, 2 H) 7.53 (m, 3 H) 7.67 (d, J=7.72 Hz, 2 H) 8.08 (d, J=8.09 Hz, 1 H) 16.24 (s, 1 H). MS (ESI-) m/z 451 (M-H).

Example 254A3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[[1,3-thiazol-2-ylmethylene]amino]quinolin-2(1H)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 1,3-thiazole-2-carbaldehyde (0.132 mL, 1.5 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 254B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1,3-thiazol-2-

ylmethylamino]quinolin-2(1H)-one

The product of Example 254A (0.030 g, 0.066 mmol) in tetrahydrofuran (1.3 mL) and methanol (0.005 mL, 0.132 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.050 mL, 0.100 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.36 (m, 2 H) 6.57 (t, J=6.62 Hz, 1 H) 7.09 (dd, J=13.60, 6.62 Hz, 2 H) 7.29 (t, J=7.54 Hz, 2 H) 7.56 (m, 2 H) 7.68 (m, 2 H) 7.97 (d, J=8.46 Hz, 1 H) 8.08 (d, J=7.35 Hz, 1 H) 16.20 (s, 1 H). MS (ESI-) m/z 452 (M-H).

Example 255A3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(2-ethyl-3-methylbutylidene)amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 2-ethyl-3-methylbutanal (0.110 mL, 0.733 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 255B3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[[2-ethyl-3-methylbutyl]amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 255A (0.031 g, 0.069 mmol) in tetrahydrofuran (1.5 mL) and methanol (0.006 mL, 0.138 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.054 mL, 0.108 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel eluted with 30% ethyl acetate/hexane to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.94 (m, 18 H) 1.36 (dd, J=11.58, 5.33 Hz, 2 H) 1.47 (m, 4 H) 1.91 (s, 2 H) 3.32 (s, 4 H) 5.87 (t, J=7.54 Hz, 2 H) 6.98 (t, J=7.54 Hz, 1 H) 7.08 (m, 2 H) 7.26 (m, 4 H) 7.38 (t, J=8.27 Hz, 1 H) 7.56 (m, 4 H) 7.66 (m, 2 H). MS (ESI-) m/z 453 (M-H).

Example 256A

5 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methylphenyl)methylene]amino]quinolin-2(1*H*)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 4-methylbenzaldehyde (0.210 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 256B

15 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methylbenzyl)amino]quinolin-2(1*H*)-one

The product of Example 256A (0.065 g, 0.142 mmol) in tetrahydrofuran (3.0 mL) and methanol (0.012 mL, 0.284 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.111 mL, 0.222 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (8.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.32 (s, 3 H) 3.87 (s, 2 H) 6.03 (s, 1 H) 7.10 (m, 1 H) 7.21 (d, J=7.72 Hz, 2 H) 7.30 (t, J=7.17 Hz, 2 H) 7.42 (d, J=7.72 Hz, 2 H) 7.56 (t, J=8.64 Hz, 2 H) 7.70 (t, J=9.38 Hz, 2 H) 8.10 (d, J=7.72 Hz, 1 H) 16.28 (m, 1 H). MS (ESI-) m/z 459 (M-H)⁻.

Example 257A

30 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylphenyl)methylene]amino]quinolin-2(1*H*)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 3-methylbenzaldehyde (0.210 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 257B3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylbenzyl)amino]quinolin-2(1*H*)-one

5 The product of Example 257A (0.038 g, 0.083 mmol) in tetrahydrofuran (1.7 mL) and methanol (0.007 mL, 0.166 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.065 mL, 0.130 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and
10 dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.35 (s, 3 H) 3.87 (s, 2 H) 6.05 (t, *J*=6.62 Hz, 1 H) 7.12 (m, 2 H) 7.31 (m, 5 H) 7.56 (t, *J*=7.54 Hz, 2 H) 7.70 (dd, *J*=11.95, 7.91 Hz, 2 H) 8.10 (d, *J*=7.72 Hz, 1 H) 16.28 (s, 1 H). MS (ESI-) *m/z* 459 (M-H).

Example 258A3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(2-methylphenyl)methylene]amino}quinolin-2(1*H*)-one

20 The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 2-methylbenzaldehyde (0.206 mL, 1.78 mmol) in *N,N*-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to
25 give the title compound.

Example 258B3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(2-methylbenzyl)amino]quinolin-2(1*H*)-one

30 The product of Example 258A (0.026 g, 0.057 mmol) in tetrahydrofuran (1.2 mL) and methanol (0.005 mL, 0.114 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.045 mL, 0.090 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration,
35 washed with water and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm

3.29 (s, 3 H) 3.97 (s, 2 H) 6.02 (t, J=6.62 Hz, 1 H) 7.08 (t, J=7.35 Hz, 1 H) 7.23 (s, 3 H) 7.29 (t, J=7.54 Hz, 2 H) 7.47 (m, 1 H) 7.55 (d, J=7.72 Hz, 2 H) 7.67 (m, 2 H) 8.10 (d, J=7.72 Hz, 1 H) 16.31 (s, 1 H). MS (ESI-) m/z 459 (M-H)⁺.

5

Example 259A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylthien-2-yl)methyl]amino}quinolin-2(1H)-one

10

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 3-methylthiophene-2-carbaldehyde (0.180 mL, 1.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

15

Example 259B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylthien-2-yl)methyl]amino}quinolin-2(1H)-one

20

The product of Example 259A (0.020 g, 0.043 mmol) in tetrahydrofuran (1.0 mL) and methanol (0.004 mL, 0.086 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.033 mL, 0.065 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 2.42 (s, 3 H) 4.10 (brs, 2 H) 7.09 (d, J=5.15 Hz, 1 H) 7.19 (brs, 1 H) 7.37 (m, 3 H) 7.58 (m, 2 H) 7.72 (m, 2 H) 8.04 (m, 1 H) 8.14 (d, J=8.09 Hz, 1 H) 16.10 (brs, 1 H). MS (ESI-) m/z 465 (M-H)⁺.

30

Example 260A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methoxyphenyl)methylene]amino}quinolin-2(1H)-one

35

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 4-methoxybenzaldehyde (0.217 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled

to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 260B

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methoxybenzyl)amino]quinolin-2(1H)-one

The product of Example 260A (0.045 g, 0.095 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.19 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.074 mL, 0.148 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with methanol/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.77 (s, 3 H) 3.82 (s, 2 H) 5.98 (s, 1 H) 6.95 (d, J=8.46 Hz, 2 H) 7.10 (t, J=7.54 Hz, 1 H) 7.30 (m, 2 H) 7.45 (d, J=8.46 Hz, 2 H) 7.56 (s, 2 H) 7.70 (t, J=9.38 Hz, 2 H) 8.10 (d, J=7.72 Hz, 1 H) 16.29 (m, 1 H). MS (ESI-) m/z 475 (M-H).

Example 261A

1-{[(5-chlorothiophen-2-yl)methylene]amino}-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 5-chlorothiophene-2-carbaldehyde (0.160 mL, 1.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 261B

1-{[(5-chlorothiophen-2-yl)methyl]amino}-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 261A (0.048 g, 0.099 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.198 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.074 mL, 0.149 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (6.0 mL), and the resulting precipitate was collected by filtration and

dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.10 (s, 2 H) 6.24 (t, J=6.43 Hz, 1 H) 7.19 (m, 1 H) 7.30 (m, 3 H) 7.43 (d, J=8.46 Hz, 1 H) 7.56 (m, 3 H) 7.67 (d, J=8.09 Hz, 1 H) 8.12 (d, J=7.72 Hz, 1 H) 15.95 (s, 1 H). MS (ESI-) m/z 485 (M-H)⁻.

Example 262A

10 1-[[(2-chloro-1,3-thiazol-5-yl)methylene]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 2-chloro-1,3-thiazole-5-carbaldehyde (0.157 mL, 1.06 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 262B

20 1-[[(2-chloro-1,3-thiazol-5-yl)methyl]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 262A (0.040 g, 0.082 mmol) in tetrahydrofuran (1.7 mL) and methanol (0.007 mL, 0.164 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.064 mL, 0.128 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (5.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.22 (m, 2 H) 6.38 (t, J=6.25 Hz, 1 H) 7.07 (t, J=7.54 Hz, 1 H) 7.28 (t, J=8.09 Hz, 2 H) 7.59 (m, 5 H) 8.08 (dd, J=8.09, 1.47 Hz, 1 H) 16.19 (s, 1 H). MS (ESI-) m/z 486 (M-H)⁻.

Example 263A

35 1-[[(3-bromophenyl)methylene]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.059 g, 0.165 mmol) was reacted with 3-

bromobenzaldehyde (0.175 mL, 1.5 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 263B

1-[(3-bromobenzyl)amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 263A (0.048 g, 0.091 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.182 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.130 mL, 0.260 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (8.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.93 (brs, 2 H) 6.17 (t, J=6.99 Hz, 1 H) 7.09 (t, J=7.54 Hz, 1 H) 7.28 (d, J=8.09 Hz, 2 H) 7.37 (d, J=7.72 Hz, 1 H) 7.54 (m, 4 H) 7.68 (m, 2 H) 7.74 (t, J=1.65 Hz, 1 H) 8.09 (dd, J=7.91, 1.29 Hz, 1 H) 16.26 (s, 1 H). MS (ESI-) m/z 524 (M-H)⁻.

Example 264A

1-[(4-bromophenyl)methylene]amino}-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 4-bromobenzaldehyde (0.278 mL, 1.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 264B

1-[(4-bromobenzyl)amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 264A (0.049 g, 0.094 mmol) in tetrahydrofuran (2.0 mL) and methanol (0.008 mL, 0.188 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.134 mL, 0.268 mmol). The reaction

was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (6.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.92 (brs, 2 H) 7.09 (t, J=6.99 Hz, 1 H) 7.28 (m, 3 H) 7.54 (m, 5 H) 7.68 (d, J=8.09 Hz, 2 H) 8.09 (dd, J=8.09, 1.47 Hz, 1 H) 16.25 (brs, 1 H). MS (ESI-) m/z 524 (M-H)⁺.

Example 265A

1-[[2-(2-bromophenyl)methylene]amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 226D (0.060 g, 0.168 mmol) was reacted with 2-bromobenzaldehyde (0.175 mL, 1.50 mmol) in N,N-dimethylacetamide (1.0 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 265B

1-[(2-bromobenzyl)amino]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The product of Example 265A (0.068 g, 0.129 mmol) in tetrahydrofuran (3.0 mL) and methanol (0.011 mL, 0.258 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.184 mL, 0.368 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (8.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.11 (brs, 2 H) 6.24 (t, J=6.80 Hz, 1 H) 7.06 (t, J=7.54 Hz, 1 H) 7.28 (m, 3 H) 7.56 (m, 3 H) 7.67 (m, 4 H) 8.08 (dd, J=7.91, 1.29 Hz, 1 H) 16.27 (s, 1 H). (ESI-) m/z 524 (M-H)⁺.

Example 266A

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[pyridin-3-

ylmethylene]amino}quinolin-2(1H)-one

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with nicotinaldehyde (0.168 mL, 1.78 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 266B3-((3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-((pyridin-3-ylmethyl)amino)quinolin-2(1H)-one

The product of Example 266A (0.062 g, 0.14 mmol) in tetrahydrofuran (2.5 mL) and methanol (0.012 mL, 0.280 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.105 mL, 0.210 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (8.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with methanol/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.99 (s, 2 H) 6.22 (t, J=6.62 Hz, 1 H) 7.08 (t, J=7.35 Hz, 1 H) 7.27 (m, 2 H) 7.40 (dd, J=7.54, 4.96 Hz, 1 H) 7.54 (m, 2 H) 7.68 (d, J=8.09 Hz, 2 H) 7.93 (m, 1 H) 8.08 (dd, J=7.72, 1.47 Hz, 1 H) 8.51 (dd, J=4.78, 1.47 Hz). (ESI-) m/z 446 (M-H)⁻

Example 267A3-((3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2-oxoquinolin-1(2H)-yl]imino)methyl)benzonitrile

The product of Example 226D (0.070 g, 0.196 mmol) was reacted with 3-formylbenzonitrile (0.080 mL, 0.610 mmol) in N,N-dimethylacetamide (1.2 mL) in a sealed tube at 110°C for 35 minutes in a microwave reactor. The reaction mixture was cooled to 25°C and concentrated. The resulting residue was triturated with ethyl acetate and filtered to give the title compound.

Example 267B3-((3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2-oxoquinolin-1(2H)-yl]amino)methyl)benzonitrile

The product of Example 267A (0.055 g, 0.117 mmol) in tetrahydrofuran (2.0 mL) and

methanol (0.010 mL, 0.234 mmol) at 0°C was treated with dropwise addition of a 2.0M solution of lithium borohydride in tetrahydrofuran (0.088 mL, 0.176 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (6.0 mL), and the resulting precipitate was collected by filtration and dried. The crude product was triturated with dichloromethane/diethyl ether and filtered to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.01 (s, 2 H) 6.25 (t, J=6.80 Hz, 1 H) 7.08 (t, J=7.35 Hz, 1 H) 7.28 (m, 2 H) 7.56 (m, 3 H) 7.68 (dd, J=8.09, 2.21 Hz, 2 H) 7.79 (d, J=8.09 Hz, 1 H) 7.86 (d, J=7.72 Hz, 1 H) 7.99 (s, 1 H) 8.09 (dd, J=7.91, 1.29 Hz, 1 H). (ESI-) m/z 470 (M-H)⁻.

Example 268A

methyl 3-[(2E)-2-benzylidenehydrazino]thiophene-2-carboxylate

A solution of methyl 3-hydrazinothiophene-2-carboxylate (Maybridge technical grade, 2.0 g, 0.11 mol) in ethanol (250 mL) at 25°C was reacted with a solution of benzaldehyde (12.32 g, 0.11 mol) in ethanol (100 mL). The mixture was stirred at 25°C for 1.5 hours and concentrated to yield 30g of a white solid. HPLC/MS show a single peak with retention time of 2.35 min. and a M+1 peak of 261. ¹H NMR (300 MHz, CDCl₃) δ ppm 3.85 (s, 3 H) 7.35 (m, 4 H) 7.64 (dd, J=8.09, 1.47 Hz, 2 H) 7.77 (s, 1 H) 10.10 (s, 1 H).

Example 268B

Methyl 3-[2-benzylidene-1-(3-ethoxy-3-oxopropanoyl)hydrazino]thiophene-2-carboxylate

The product of Example 185A (26.4g, 0.101 mol) was reacted with ethyl chloromalonate (18.3 g, 0.121 mol) in toluene (400 mL), stirred at reflux for 4 hours, allowing HCl gas to bubble out of the condenser. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was chromatographed on silica gel eluting with 3:1 hexanes/ethyl acetate to give the title compound (37.1 g, 98%).

Example 268C

Ethyl 7-hydroxy-5-oxo-4-{[phenylmethylene]amino}-4,5-dihydrothieno[3,2-b]pyridine-6-carboxylate

A solution of the product of Example 268B (37.8 g, 0.101 mol) in ethanol (0.5 L) under nitrogen was reacted with sodium ethoxide in ethanol (21% by weight, 32.8 g, 0.104

mol) at room temperature. The mixture was slowly warmed to 50°C and stirred for 1 hour at 40-50°C, cooled to 25°C, partitioned between ethyl acetate and water, and acidified to pH 4 with 1M hydrochloric acid. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give the title compound (12.0 g, 35%). ¹H NMR (300 MHz, CDCl₃) δ ppm 1.47 (t, *J*=7.17 Hz, 3 H) 4.52 (q, *J*=7.23 Hz, 2 H) 7.33 (d, *J*=5.15 Hz, 1 H) 7.50 (m, 3 H) 7.75 (d, *J*=5.52 Hz, 1 H) 7.88 (dd, *J*=7.72, 1.84 Hz, 2 H) 9.44 (s, 1 H) 14.16 (s, 1 H).

Example 268D

4-amino-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268C (2.29 g, 6.69 mmol) was reacted with 2-aminobenzenesulfonamide (1.15 g, 6.69 mmol) in toluene (60 mL), and stirred at reflux for 5 hours. The reaction was cooled to 25°C and the resulting precipitate was collected by filtration and dried (1.95g, 62%). The resulting solid (1.95 g, 4.2 mmol) was reacted with 10% aqueous KOH (60 mL) at reflux for 24 hours, cooled to 25°C and acidified with concentrated hydrochloric acid to pH 2. The resulting solid was collected by filtration, washed repeatedly with water and dried to provide the title compound (1.5 g, 98%). (Any sodium salt made?) ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 6.12 (s, 2 H) 7.49 (d, *J*=5.52 Hz, 1 H) 7.57 (m, 2 H) 7.79 (t, *J*=7.17 Hz, 1 H) 7.93 (d, *J*=7.72 Hz, 1 H) 8.34 (d, *J*=5.52 Hz, 1 H) 14.33 (s, 1 H) 14.68 (s, 1 H).

Example 269A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-([2-methylpropylidene]amino)thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10g, 0.27 mmol) was reacted with 2-methylpropionaldehyde (0.20g, 2.77 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 135°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with a mixture of 25% ethyl acetate in hexanes and filtered to give the title compound as a solid (0.073 g, 65%). MS (APCI+) *m/z* 417 (*M*+*H*)⁺.

Example 269B

6-(1,1-Dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(isobutylamino)thieno[3,2-

b]pyridin-5(4H)-one

The product of Example 269A (0.073 g, 0.18 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.20 mL, 0.40 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was suspended in tetrahydrofuran (10 mL) and adsorbed onto approximately 5g of silica gel and evaporated. The product was eluted with methanol in chloroform. Product containing fractions were combined and evaporated under vacuum to give the title compound (0.032 g, 42%). MS (ESI-) m/z 417 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.01 (d, J=6.62 Hz, 6 H) 1.88 (m, 1 H) 2.83 (s, 2 H) 6.60 (s, 1 H) 7.41 (d, J=4.04 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.65 (d, J=8.46 Hz, 1 H) 7.77 (t, J=7.91 Hz, 1 H) 7.93 (d, J=7.72 Hz, 1 H) 8.35 (d, J=4.78 Hz, 1 H) 14.21 (s, 1 H) 14.82 (s, 1 H).

Example 270A6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-{[(3S)-3-methylcyclopentylidene]amino}thieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.065 g, 0.18 mmol) was reacted with (3S)-3-methylcyclopentanone (0.54 g, 5.6 mmol) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 90 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with ethyl acetate/hexane (2:1) and filtered to give the title compound.

Example 270B6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-{[(3S)-3-methylcyclopentyl]amino}thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.060 g, 0.14 mmol) in tetrahydrofuran (4 mL) and methanol (0.012 mL, 0.3 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.12 mL, 0.24 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to dichloromethane/methanol (99:1). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.01 (m, 3 H) 1.69 (m, 7 H) 3.76 (m, 1

H) 5.75 (s, 1 H) 7.19 (m, 3 H) 7.54 (m, 1 H) 7.65 (d, J=7.72 Hz, 1 H) 7.74 (d, J=6.25 Hz, 1 H) 15.91 (s, 1 H). MS (ESI-) m/z 443 (M-H)⁻.

Example 271A

4-{[1-cyclopropylethylidene]amino}-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-
hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.065 g, 0.18 mmol) was reacted with 1-cyclopropylethanone (0.54 g, 6.4 mmol) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 120 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with ethyl acetate/hexane (2:1) and filtered to give the title compound.

Example 271B

4-{[1-cyclopropylethyl]amino}-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-
hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.058 g, 0.14 mmol) in tetrahydrofuran (4 mL) and methanol (0.012 mL, 0.3 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.12 mL, 0.24 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with dichloromethane to dichloromethane/methanol (99:1) to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.05 (m, 8 H) 2.44 (m, 1 H) 5.81 (d, J=2.57 Hz, 1 H) 7.23 (m, 3 H) 7.53 (m, 1 H) 7.64 (d, 1=7.72 Hz, 1 H) 7.74 (s, br, 1 H) 15.95 (s, 1 H). MS (ESI-) m/z 429 (M-H)⁻.

Example 272A

4-[(butylideneamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with butyraldehyde (0.5 g, 6.9 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.075g, 65%).

Example 272B4-(butylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

5 The product of Example 269A (0.075 g, 0.18 mmol) in tetrahydrofuran (4 mL) and methanol (0.029 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude
10 product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.90 (t, J=7.17 Hz, 3 H) 1.39 (dd, J=15.08, 7.35 Hz, 2 H) 1.50 (m, 2 H) 3.02 (t, J=6.43 Hz, 2 H) 6.65 (s, 1 H) 7.43 (d, J=5.15 Hz, 1 H) 7.55 (t, J=7.72 Hz, 1 H) 7.64 (d, J=8.09 Hz, 1 H) 7.77 (t, J=7.72 Hz, 1 H) 7.92 (d, J=8.09 Hz, 1 H) 8.34 (d, J=5.15 Hz, 1 H) 14.21 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) *m/z* 417 (M-H)⁻.

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Example 273A6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(2-ethylbutylidene)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

 The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 2-ethylbutanal (0.5 g, 5.2 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes
25 in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.082g, 68%).

30

Example 273B6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(2-ethylbutyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

 The product of Example 269A (0.82 g, 0.18 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1
35 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title

compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.90 (t, J=7.17 Hz, 6 H) 1.45 (m, 5 H) 2.94 (m, J=4.78 Hz, 2 H) 6.53 (s, 1 H) 7.38 (d, J=5.52 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.65 (d, J=8.09 Hz, 1 H) 7.77 (t, J=8.46 Hz, 1 H) 7.92 (d, J=7.72 Hz, 1 H) 8.36 (d, J=5.52 Hz, 1 H) 14.19 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) m/z 445(M-H)⁻.

Example 274A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[pentylideneamino]thieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with pentanal (0.5 g, 5.0 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.081g, 70%).

Example 274B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(pentylamino)thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.081 g, 0.19 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.88 (t, J=6.99 Hz, 3 H) 1.34 (m, 4 H) 1.53 (m, 2 H) 3.01 (t, J=6.62 Hz, 2 H) 6.64 (s, 1 H) 7.43 (d, J=5.15 Hz, 1 H) 7.55 (t, J=7.72 Hz, 1 H) 7.64 (d, J=8.09 Hz, 1 H) 7.78 (t, J=7.91 Hz, 1 H) 7.93 (d, J=8.09 Hz, 1 H) 8.35 (d, J=5.52 Hz, 1 H) 14.21 (s, 1 H) 14.81 (s, 1 H). MS (ESI-) m/z 431 (M-H)⁻.

Example 275A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-{[3-methylbutylidene]amino}thieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3-methylbutanal (0.5 g, 5.8 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.083g, 71%).

Example 275B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbutyl)amino]thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.083 g, 0.19 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.90 (d, J=6.62 Hz, 6 H) 1.44 (q, J=7.11 Hz, 2 H) 1.70 (m, 1 H) 3.03 (t, J=6.99 Hz, 2 H) 6.61 (s, 1 H) 7.43 (d, J=5.15 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.65 (d, J=8.09 Hz, 1 H) 7.77 (t, J=7.72 Hz, 1 H) 7.92 (d, J=7.72 Hz, 1 H) 8.35 (d, J=5.52 Hz, 1 H) 14.20 (s, 1 H) 14.81 (s, 1 H). MS (ESI-) m/z 431 (M-H).

Example 276A

4-[(3,3-dimethylbutylidene)amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3,3-dimethylbutanal (0.5 g, 5.0 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.072g, 77%).

Example 276B

4-[(3,3-dimethylbutyl)amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.072 g, 0.21 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium

borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.89 (s, 9 H) 1.49 (dd, J=9.56, 6.99 Hz, 2 H) 3.03 (m, 2 H) 6.61 (s, 1 H) 7.43 (d, J=5.52 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.66 (d, J=7.72 Hz, 1 H) 7.77 (m, 1 H) 7.92 (d, J=8.09 Hz, 1 H) 8.35 (d, J=5.52 Hz, 1 H) 14.19 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) *m/z* 445 (M-H)⁻.

Example 277A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylphenyl)methylene]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3-methylbenzaldehyde (0.5 g, 4.2 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.092, 73%).

Example 277B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.090 g, 0.2 mmol) in tetrahydrofuran (4 mL) and methanol (0.015 mL, 0.4 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.29 (s, 3 H) 4.15 (s, 2 H) 6.94 (s, 1 H) 7.22 (m, 4 H) 7.30 (d, J=5.15 Hz, 1 H) 7.56 (t, J=7.72 Hz, 1 H) 7.68 (d, J=8.46 Hz, 1 H) 7.79 (t, J=6.99 Hz, 1 H) 7.94 (d, J=7.72 Hz, 1 H) 8.24 (d, J=5.15 Hz, 1 H) 14.26 (s, 1 H) 14.84 (s, 1 H). MS (ESI-) *m/z* 465 (M-H)⁻.

Example 278A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methylphenyl)methylene]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

5 The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 2-methylbenzaldehyde (0.5 g, 4.2 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.072g, 57%).

Example 278B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methylbenzyl)amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

15 The product of Example 269A (0.072 g, 0.15 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.45 (s, 3 H) 4.21 (s, 2 H) 6.92 (s, 1 H) 7.15 (m, 5 H) 7.56 (t, J=7.72 Hz, 1 H) 7.67 (d, J=8.09 Hz, 1 H) 7.79 (t, J=7.72 Hz, 1 H) 7.94 (d, J=7.72 Hz, 1 H) 8.17 (d, J=5.52 Hz, 1 H) 14.22 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) *m/z* 465 (M-H)⁻.

Example 279A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(4-methylphenyl)methylene]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

30 The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 4-methylbenzaldehyde (0.5 g, 4.2 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.10 g, 81%).

Example 279B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(4-methylbenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.10 g, 0.22 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 2.27 (s, 3 H) 4.14 (s, 2 H) 6.92 (s, 1 H) 7.13 (d, *J*=8.09 Hz, 2 H) 7.28 (d, *J*=2.94 Hz, 1 H) 7.30 (d, *J*=5.88 Hz, 2 H) 7.56 (t, *J*=7.72 Hz, 1 H) 7.67 (d, *J*=8.46 Hz, 1 H) 7.79 (t, *J*=7.72 Hz, 1 H) 7.94 (d, *J*=7.72 Hz, 1 H) 8.22 (d, *J*=5.52 Hz, 1 H) 14.21 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) *m/z* 465 (M-H)⁻.

Example 280A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbut-2-enylidene)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3-methylbut-2-enal (0.5 g, 5.9 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 130°C for 40 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.093g, 80%).

Example 280B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbut-2-enyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.093 g, 0.22 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.51 (s, 3 H) 1.61 (s, 3 H) 3.64 (d, *J*=6.99 Hz, 2 H) 5.32 (t, *J*=8.09 Hz, 1 H) 6.65 (s, 1 H) 7.43 (d, *J*=5.52 Hz, 1 H) 7.55 (t, *J*=7.54

Hz, 1 H) 7.64 (d, J=8.46 Hz, 1 H) 7.78 (t, J=7.17 Hz, 1 H) 7.92 (d, J=7.72 Hz, 1 H) 8.32 (m, 1 H) 14.21 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) m/z 429 (M-H)⁺.

5

Example 281A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[propylideneamino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with propionaldehyde (0.5 g, 8.6 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 120°C for 90 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.073g, 67%).

15

Example 281B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(propylamino)thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.073 g, 0.18 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.95 (t, J=7.35 Hz, 3 H) 1.54 (m, 2 H) 2.99 (t, J=6.99 Hz, 2 H) 6.66 (s, 1 H) 7.44 (d, J=5.15 Hz, 1 H) 7.55 (t, J=7.54 Hz, 1 H) 7.64 (d, J=8.09 Hz, 1 H) 7.78 (t, J=7.17 Hz, 1 H) 7.93 (d, J=7.72 Hz, 1 H) 8.35 (d, J=5.15 Hz, 1 H) 14.20 (s, 1 H) 14.81 (s, 1 H). MS (ESI-) m/z 403 (M-H)⁺.

30

Example 282A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-{[pyridin-4-ylmethylene]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

35

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with isonicotinaldehyde (0.5 g, 4.7 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and

concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.093g, 76%).

Example 282B

5 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-4-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.093 g, 0.21 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1
10 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 4.39 (s, 2 H) 7.34 (d, J=5.15 Hz, 1
15 H) 7.42 (s, 1 H) 7.56 (t, J=7.72 Hz, 1 H) 7.63 (d, J=8.09 Hz, 1 H) 7.79 (m, J=7.72, 7.72 Hz, 3 H) 7.94 (d, J=7.72 Hz, 1 H) 8.27 (d, J=5.15 Hz, 1 H) 8.52 (d, J=6.62 Hz, 2 H) 14.15 (s, 1 H) 14.87 (s, 1 H). MS (ESI-) *m/z* 452 (M-H)⁺.

Example 283A

20 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-3-ylmethylene)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with nicotinaldehyde
25 (0.5 g, 4.7 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.102g, 84%).

Example 283B

30 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-3-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.102 g, 0.23 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium
35 borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude

product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.33 (s, 2 H) 7.28 (d, J=5.52 Hz, 1 H) 7.36 (s, 1 H) 7.61 (m, 3 H) 7.79 (t, J=7.17 Hz, 1 H) 7.94 (d, J=8.09 Hz, 1 H) 8.20 (d, J=11.03 Hz, 1 H) 8.27 (d, J=5.51 Hz, 1 H) 8.49 (d, J=5.51 Hz, 1 H) 8.64 (s, 1 H) 14.14 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) m/z 452 (M-H)⁻.

Example 284A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-2-ylmethylene)amino]thieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 2-pyridinecarboxaldehyde (0.5 g, 4.7 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.071 g, 58%).

Example 284B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-2-ylmethyl)amino]thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.071 g, 0.16 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 5% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.65 (s, 2 H) 7.25 (d, J=5.15 Hz, 1 H) 7.45 (s, 1 H) 7.59 (m, 3 H) 7.78 (t, J=7.91 Hz, 1 H) 7.93 (d, J=7.72 Hz, 2 H) 8.16 (t, J=7.72 Hz, 1 H) 8.24 (d, J=5.15 Hz, 1 H) 8.72 (d, J=5.51 Hz, 1 H) 14.10 (s, 1 H) 14.87 (s, 1 H). MS (ESI-) m/z 452(M-H)⁻.

Example 285A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-

methoxyphenyl)methylene]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3-methoxybenzaldehyde (0.5 g, 3.7 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.093 g 72%).

Example 285B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methoxybenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.093 g, 0.19 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.73 (s, 3 H) 4.17 (s, 2 H) 6.84 (m, 1 H) 6.98 (m, 3 H) 7.22 (d, *J*=8.09 Hz, 1 H) 7.26 (d, *J*=5.15 Hz, 1 H) 7.56 (t, *J*=7.17 Hz, 1 H) 7.67 (d, *J*=8.09 Hz, 1 H) 7.79 (t, *J*=8.46 Hz, 1 H) 7.94 (d, *J*=7.72 Hz, 1 H) 8.22 (d, *J*=5.15 Hz, 1 H) 14.21 (s, 1 H) 14.84 (s, 1 H). MS (ESI-) *m/z* 481 (M-H)⁻.

Example 286A

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(3-furylmethylene]amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.10 g, 0.27 mmol) was reacted with 3-furaldehyde (0.5 g, 5.2 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.103 g, 87%).

Example 286B

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(3-furylmethyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.103 g, 0.23 mmol) in tetrahydrofuran (4 mL) and

methanol (0.030 mL, 0.8 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.200 mL, 0.4 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.08 (s, 2 H) 6.59 (s, 1 H) 6.95 (s, 1 H) 7.32 (d, J=5.15 Hz, 1 H) 7.58 (m, 3 H) 7.66 (d, J=8.09 Hz, 1 H) 7.79 (t, J=8.46 Hz, 1 H) 7.93 (d, J=7.72 Hz, 1 H) 8.24 (d, J=5.52 Hz, 1 H) 14.21 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) m/z 441 (M-H)⁻.

Example 287A

3-([6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-5-oxothienof[3,2-b]pyridin-4(5H)-yl]imino)methyl)benzonitrile

The product of Example 268D (0.100 g, 0.27 mmol) was reacted with 3-formylbenzonitrile (0.362 g, 2.75 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.088g, 69%).

Example 287B

3-([6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-5-oxothienof[3,2-b]pyridin-4(5H)-yl]amino)methyl)benzonitrile

The product of Example 269A (0.088 g, 0.19 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.26 (s, 2 H) 7.21 (s, 1 H) 7.29 (d, J=5.15 Hz, 1 H) 7.55 (m, 2 H) 7.65 (d, J=8.09 Hz, 1 H) 7.78 (m, 3 H) 7.94 (m, 2 H) 8.22 (d, J=5.52 Hz, 1 H) 14.19 (s, 1 H) 14.83 (s, 1 H). MS (ESI-) m/z 476(M-H)⁻.

Example 288A6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(thien-3-ylmethylene)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

5 The product of Example 268D (0.10 g, 0.27 mmol) was reacted with thiophene-3-carbaldehyde (0.5 g, 4.5 mmol) in *N,N*-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.077 g, 63%).

Example 288B6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(thien-3-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

10 The product of Example 269A (0.077 g, 0.17 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.150 mL, 0.3 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to pH of approximately 2-4, diluted with water (25 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 4.22 (s, 2 H) 7.01 (s, 1 H) 7.20 (dd, J=4.96, 1.29 Hz, 1 H) 7.23 (d, J=5.52 Hz, 1 H) 7.40 (d, J=1.84 Hz, 1 H) 7.48 (dd, J=4.78, 2.94 Hz, 1 H) 7.56 (t, J=7.17 Hz, 1 H) 7.67 (d, J=7.72 Hz, 1 H) 7.79 (t, J=7.72 Hz, 1 H) 7.94 (d, J=7.72 Hz, 1 H) 8.21 (d, J=5.15 Hz, 1 H) 14.21 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) *m/z* 457 (M-H)-.

Example 289A4-(cyclobutylideneamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

30 The product of Example 268D (0.10 g, 0.27 mmol) was reacted with cyclobutanone (1.0 g, 14.3 mmol) in *N,N*-dimethylacetamide (2 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.086 g 77%).

Example 289B4-(cyclobutylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.077 g, 0.21 mmol) in tetrahydrofuran (4 mL) and methanol (0.030 mL, 0.8 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.200 mL, 0.4 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid to pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.81 (m, 6 H) 3.85 (m, 1 H) 6.84 (s, 1 H) 7.49 (d, *J*=5.15 Hz, 1 H) 7.55 (t, *J*=7.91 Hz, 1 H) 7.62 (d, *J*=8.09 Hz, 1 H) 7.78 (t, *J*=7.91 Hz, 1 H) 7.93 (d, *J*=8.09 Hz, 1 H) 8.33 (d, *J*=5.15 Hz, 1 H) 14.21 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) *m/z* 415 (M-H)⁻.

Example 290A6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-
{[phenylmethylene]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.115 g, 0.30 mmol) was reacted with benzaldehyde (0.32 g, 3.0 mmol) in *N,N*-dimethylacetamide (2 mL) in a sealed tube at 135°C for 50 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with 0.1 M HCl (20 mL) and filtered to give the title compound.

Example 290B4-(benzylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.116 g, 0.257 mmol) in tetrahydrofuran (5 mL) and methanol (0.021 mL, 0.514 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.19 mL, 0.386 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 3.97 (d, *J*=5.54 Hz, 2 H) 6.17 (t, *J*=6.43 Hz, 1 H) 7.08 (d, *J*=5.52 Hz, 1 H) 7.21 (d, *J*=8.09 Hz, 1 H) 7.33 (m, 4 H) 7.47

(d, J=6.62 Hz, 2 H) 7.55 (t, J=6.99 Hz, 1 H) 7.66 (d, J=7.35 Hz, 1 H) 7.73 (d, J=5.52 Hz, 1 H) 15.92 (s, 1 H). MS (ESI-) m/z 451 (M-H)⁻.

5

Example 291A

4-[(cyclohexylmethylene)amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.115 g, 0.30 mmol) was reacted with cyclohexanecarbaldehyde (0.336 g, 3.0 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with 0.1 M HCl (20 mL) and filtered to give the title compound.

15

Example 291B

4-[(cyclohexylmethyl)amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.12 g, 0.26 mmol) in tetrahydrofuran (5 mL) and methanol (0.021 mL, 0.52 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.195 mL, 0.39 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (15 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 97:3 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.04 (m, 2 H) 1.23 (m, 3 H) 1.52 (m, 1 H) 1.68 (m, 3 H) 1.87 (m, 2 H) 2.69 (m, 2 H) 5.95 (t, J=7.17 Hz, 1 H) 7.07 (d, J=5.52 Hz, 1 H) 7.19 (d, J=8.09 Hz, 1 H) 7.26 (t, J=7.72 Hz, 1 H) 7.53 (t, J=7.17 Hz, 1 H) 7.65 (d, J=6.99 Hz, 1 H) 7.78 (d, J=5.15 Hz, 1 H) 15.91 (s, 1 H). MS (APCT⁺) m/z 459 (M+H)⁺.

30

Example 292A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1,3-thiazol-5-ylmethylene]amino]thieno[3,2-b]pyridin-5(4H)-one

35

The product of Example 268D (0.115 g, 0.30 mmol) was reacted with 1,3-thiazole-5-carbaldehyde (0.35 g, 3.0 mmol) in N,N-dimethylacetamide (3 mL) in a sealed tube at 140°C

for 80 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with 0.1 M HCl (20 mL) and filtered to give the title compound.

5

Example 292B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(1,3-thiazol-5-ylmethyl)amino]thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.137 g, 0.30 mmol) in tetrahydrofuran (7 mL) and methanol (0.025 mL, 0.6 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.225 mL, 0.45 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 95:5 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.34 (m, 2 H) 6.45 (t, J=5.52 Hz, 1 H) 6.97 (d, J=5.15 Hz, 1 H) 7.20 (d, J=8.09 Hz, 1 H) 7.27 (t, J=7.54 Hz, 1 H) 7.54 (t, J=7.17 Hz, 1 H) 7.66 (d, J=7.72 Hz, 1 H) 7.70 (d, J=5.52 Hz, 1 H) 7.79 (s, 1 H) 9.02 (s, 1 H) 15.87 (s, 1 H). MS (ESI-) m/z 458 (M-H).

20

Example 293A

4-[(3-bromophenyl)methylene]amino}-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythienof[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.115 g, 0.30 mmol) was reacted with 3-bromobenzaldehyde (0.555 g, 3.0 mmol) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 30 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with ethyl acetate (3 mL) and filtered to give the title compound.

30

Example 293B

4-[(3-bromobenzyl)amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythienof[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.13 g, 0.245 mmol) in tetrahydrofuran (4 mL) and methanol (0.015 mL, 0.36 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.15 mL, 0.30 mmol). The reaction was stirred at 25°C for 2 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with

water (15 mL), and the resulting precipitate was collected by filtration and dried to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.02 (m, 2 H) 6.27 (t, J=6.25 Hz, 1 H) 7.08 (d, J=5.15 Hz, 1 H) 7.20 (d, J=8.46 Hz, 1 H) 7.28 (t, J=7.72 Hz, 1 H) 7.32 (t, J=6.99 Hz, 1 H) 7.46 (d, J=7.72 Hz, 1 H) 7.54 (m, 2 H) 7.67 (m, 2 H) 7.73 (d, J=5.15 Hz, 1 H) 15.90 (s, 1 H). MS (ESI-) m/z 529/531 (M-H)⁺.

Example 294A

4-(cyclohexylideneamino)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.054 g, 0.15 mmol) was reacted with cyclohexanone (0.44 g, 4.5 mmol) in N,N-dimethylacetamide (1 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 294B

4-(cyclohexylamino)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.051 g, 0.115 mmol) in tetrahydrofuran (5 mL) and methanol (0.01 mL, 0.23 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.090 mL, 0.175 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 97:3 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.16 (m, 5 H) 1.59 (m, 5 H) 3.01 (m, 1 H) 5.75 (d, J=3.31 Hz, 1 H) 7.15 (d, J=5.52 Hz, 1 H) 7.19 (d, J=7.72 Hz, 1 H) 7.26 (t, J=7.54 Hz, 1 H) 7.54 (m, 1 H) 7.65 (d, J=7.72 Hz, 1 H) 7.72 (d, J=5.52 Hz, 1 H) 15.93 (s, 1 H). MS (ESI-) m/z 443 (M-H)⁺.

Example 295A

4-(cyclopentylideneamino)-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-

hydroxythienof[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.054 g, 0.15 mmol) was reacted with cyclopentanone (0.95 g, 11.3 mmol) in *N,N*-dimethylacetamide (1 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 295B4-(cyclopentylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythienof[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.040 g, 0.09 mmol) in tetrahydrofuran (3 mL) and methanol (0.008 mL, 0.19 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.07 mL, 0.14 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.54 (m, 6 H) 1.74 (m, 2 H) 3.75 (m, 1 H) 5.77 (d, *J*=3.68 Hz, 1 H) 7.12 (d, *J*=5.15 Hz, 1 H) 7.19 (d, *J*=7.72 Hz, 1 H) 7.26 (t, *J*=7.17 Hz, 1 H) 7.54 (m, 1 H) 7.64 (d, *J*=7.72 Hz, 1 H) 7.74 (d, *J*=5.52 Hz, 1 H) 15.91 (s, 1 H). MS (ESI-) *m/z* 429 (M-H)⁻.

Example 296A4-(cycloheptylideneamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythienof[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.054 g, 0.15 mmol) was reacted with cycloheptanone (0.84 g, 7.5 mmol) in *N,N*-dimethylacetamide (1 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 296B4-(cycloheptylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythienof[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.06 g, 0.13 mmol) in tetrahydrofuran (4 mL) and

methanol (0.011 mL, 0.26 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.10 mL, 0.2 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.35 (m, 4 H) 1.50 (m, 4 H) 1.64 (m, 3 H) 1.86 (m, 1 H) 2.56 (m, 1 H) 5.62 (d, J=2.94 Hz, 1 H) 7.12 (d, J=5.52 Hz, 1 H) 7.19 (d, J=8.09 Hz, 1 H) 7.26 (t, J=7.54 Hz, 1 H) 7.53 (m, 1 H) 7.64 (d, J=7.72 Hz, 1 H) 7.72 (d, J=5.15 Hz, 1 H) 15.92 (s, 1 H). MS (ESI-) m/z 457 (M-H).

Example 297A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-([3-methylcyclohexylidene]amino)thieno[3,2-b]pyridin-5(4H)-one

The product of Example 268D (0.054 g, 0.15 mmol) was reacted with 3-methylcyclohexanone (1.26 g, 11.25 mmol) in N,N-dimethylacetamide (1 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 297B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-([3-methylcyclohexyl]amino)thieno[3,2-b]pyridin-5(4H)-one

The product of Example 269A (0.060 g, 0.13 mmol) in tetrahydrofuran (4 mL) and methanol (0.011 mL, 0.26 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.1 mL, 0.20 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.86 (m, 4 H) 1.08 (m, 1 H) 1.29 (m, 3 H) 1.60 (m, 3 H) 1.93 (m, 1 H) 3.04 (m, 1 H) 5.76 (d, J=3.31 Hz, 1 H) 7.14 (d, J=5.52 Hz, 1 H) 7.19 (d, J=8.46 Hz, 1 H) 7.26 (t, J=7.54 Hz, 1 H) 7.52 (dt, J=8.46, 1.47 Hz, 1 H) 7.65 (d, J=8.09 Hz, 1 H) 7.73 (t, J=5.15 Hz, 1 H) 15.93 (s, 1 H). MS (ESI-) m/z 457 (M-H).

Example 298A

5 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3*R*)-3-
methylcyclohexylidene]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.073 g, 0.2 mmol) was reacted with (3*R*)-3-methylcyclohexanone (1.12 g, 10.0 mmol) in *N,N*-dimethylacetamide (2 mL) in a sealed tube at 135°C for 45 minutes in a microwave reactor. The reaction was cooled to 25°C and
10 concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 298B

15 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3*R*)-3-
methylcyclohexyl]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.06 g, 0.13 mmol) in tetrahydrofuran (6 mL) and methanol (0.011 mL, 0.26 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.1 mL, 0.2 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with
20 water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.86 (m, 4 H) 1.08 (m, 1 H) 1.29 (m, 3 H) 1.60 (m, 3 H) 1.93 (m, 1 H) 3.04 (m, 1 H) 5.76 (d, *J*=3.31 Hz, 1 H) 7.14 (d, *J*=5.52 Hz, 1 H) 7.19 (d, *J*=8.46 Hz, 1 H) 7.26 (t, *J*=7.54 Hz, 1 H) 7.52 (dt, *J*=8.46, 1.47 Hz, 1 H) 7.65 ((d, *J*=8.09 Hz, 1 H) 7.73 (t, *J*=5.15 Hz, 1 H) 15.93 (s, 1 H). MS (ESI-) *m/z* 457 (M-H)⁻.
25

Example 299A

30 6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(1-ethylpropylidene)amino]-7-
hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 268D (0.073 g, 0.2 mmol) was reacted with pentan-3-one (0.86 g, 10.0 mmol) in *N,N*-dimethylacetamide (2 mL) in a sealed tube at 135°C for 40
35 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 299B6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(1-ethylpropyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

5 The product of Example 269A (0.08 g, 0.18 mmol) in tetrahydrofuran (7 mL) and methanol (0.015 mL, 0.36 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.135 mL, 0.27 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude
10 product was chromatographed on silica gel with 98:2 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.87 (m, 6 H) 1.29 (m, 4 H) 3.03 (m, 1 H) 5.76 (d, J=3.68 Hz, 1 H) 7.12 (d, J=5.52 Hz, 1 H) 7.19 (d, J=8.46 Hz, 1 H) 7.26 (t, J=6.99 Hz, 1 H) 7.54 (m, 1 H) 7.65 (d, J=7.72 Hz, 1 H) 7.74 (d, J=5.15 Hz, 1 H)
15 15.95 (s, 1 H). MS (ESI-) *m/z* 431 (M-H).

Example 300A6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1-phenylethylidene]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

20 The product of Example 268D (0.073 g, 0.2 mmol) was reacted with 1-phenylethanone (1.2 g, 10.0 mmol) in *N,N*-dimethylacetamide (2 mL) in a sealed tube at 135°C for 75 minutes in a microwave reactor. The reaction was cooled to 25°C and
25 concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

Example 300B6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1-phenylethyl]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one

30 The product of Example 269A (0.046 g, 0.10 mmol) in tetrahydrofuran (5 mL) and methanol (0.005 mL, 0.12 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.06 mL, 0.12 mmol). The reaction was stirred at 25°C for 3 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with
35 water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 99:1 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the

procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.26 (m, 3 H) 4.49 (m, 1 H) 5.90 (m, 1 H) 7.20 (d, J=8.09 Hz, 1 H) 7.27 (t, J=8.46 Hz, 2 H) 7.30 (m, 5 H) 7.54 (m, 2 H) 7.66 (d, J=8.09 Hz, 1 H) 15.93 (s, 1 H). MS (ESI-) m/z 465 (M-H)⁺.

5

Example 301A

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1-methylbutylidene]amino]thieno[3,2-b]pyridin-5(4H)-one

10

The product of Example 268D (0.073 g, 0.2 mmol) was reacted with pentan-2-one (0.9 g, 10.4 mmol) in N,N-dimethylacetamide (2 mL) in a sealed tube at 135°C for 60 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether (3 mL) and filtered to give the title compound.

15

Example 301B

6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1-methylbutyl]amino]thieno[3,2-b]pyridin-5(4H)-one

20

The product of Example 269A (0.070 g, 0.16 mmol) in tetrahydrofuran (mL) and methanol (0.013 mL, 0.32 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.12 mL, 0.24 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1M hydrochloric acid a pH of approximately 2-4, diluted with water (10 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 99:1 dichloromethane/methanol to give the title compound. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.87 (m, 6 H) 1.30 (m, 4 H) 3.25 (m, 1 H) 5.74 (d, J=3.68 Hz, 1 H) 7.13 (d, J=5.15 Hz, 1 H) 7.19 (d, J=8.09 Hz, 1 H) 7.26 (t, J=7.54 Hz, 1 H) 7.54 (dd, J=8.09, 1.47 Hz, 1 H) 7.65 (d, J=7.72 Hz, 1 H) 7.73 (d, J=5.52 Hz, 1 H) 15.94 (s, 1 H). MS (ESI-) m/z 431 (M-H)⁺.

30

Example 303A

4-[[cyclopropylmethylene]amino]-6-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

35

The product of Example 268D (0.15 g, 0.41 mmol) was reacted with cyclopropanecarbaldehyde (1.0 g, 14 mmol) in N,N-dimethylacetamide (3 mL) in a sealed

tube at 120°C for 90 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under vacuum. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.104g, 60%).

5 Example 303B

4-[(cyclopropylmethyl)amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 269A (0.104 g, 0.25 mmol) in tetrahydrofuran (4 mL) and methanol (0.020 mL, 0.5 mmol) at 0°C was treated dropwise with a 2.0M solution of lithium borohydride in tetrahydrofuran (0.200 mL, 0.4 mmol). The reaction was stirred at 25°C for 1
10 hour, acidified with 1M hydrochloric acid to pH of approximately 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 1% methanol in chloroform to give the title compound. The sodium salt of the title compound was prepared according to the procedure
15 of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.06 (m, 2 H) 0.36 (m, 2 H) 0.96 (m, 1 H) 2.92 (d, *J*=6.99 Hz, 2 H) 6.75 (s, 1 H) 7.53 (d, *J*=5.52 Hz, 1 H) 7.55 (m, 1 H) 7.63 (d, *J*=8.09 Hz, 1 H) 7.77 (m, 1 H) 7.92 (d, *J*=7.72 Hz, 1 H) 8.33 (d, *J*=5.52 Hz, 1 H) 14.19 (s, 1 H) 14.82 (s, 1 H). MS (ESI-) *m/z* 415 (M-H).

20 Example 304A

4-(benzyloxy)-2-fluoro-1-nitrobenzene

25 3-Fluoro-4-nitro-phenol (10 g, 0.064 mol) was reacted with benzyl bromide (8.3 mL, 0.070 mol), cesium carbonate (22.7 g, 0.07 mol), and tetrabutyl ammonium iodide (0.05 g) in N,N-dimethylformamide (100 mL) at 25°C for 18 hr. The reaction mixture was poured into distilled water (500 mL) and stirred for 10 minutes. The reaction mixture was extracted with ethyl acetate (3 X 200 mL). The combined organic extracts were washed with brine, dried
30 over anhydrous sodium sulfate, filtered and solvent removed under reduced pressure to give the title compound as a light yellow solid (15 g). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 5.27 (s, 2 H) 7.06 (dd, *J*=9.56, 2.57 Hz, 1 H) 7.29 (dd, *J*=13.60, 2.57 Hz, 1 H) 7.44 (m, 5 H) 8.17 (t, *J*=9.19 Hz, 1 H). ESI *m/z* (M+H)⁺: 248

35 Example 304B

4-(benzyloxy)-2-(benzylthio)-1-nitrobenzene

A slurry of the product of Example 304A (15g, 0.061 mol) in ethanol (100 mL), was

treated with sodium carbonate (6.41 g, 0.061 mol) and benzyl mercaptan (7.5 mL, 0.058 mol) in water (50 mL). The reaction mixture was refluxed for 5 hours, cooled to 25°C and poured into of distilled water (800 mL). The resulting slurry was stirred for 1 hour at 25°C and filtered. The resulting yellow solid was washed with water and dried in a vacuum oven at 50°C to give the title compound (20.53 g). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.35 (s, 2 H) 5.27 (s, 2 H) 7.02 (dd, *J*=9.19, 2.57 Hz, 1 H) 7.16 (d, *J*=2.57 Hz, 1 H) 7.40 (m, 10 H) 8.24 (d, *J*=9.19 Hz, 1 H). ESI m/z (M+H)⁺: 352

Example 304C

5-(benzyloxy)-2-nitrobenzenesulfonamide

A slurry of the product of Example 304B (5g, 0.014 mol) in glacial acetic acid (50 mL) and water (5.5 mL) at 0°C was bubbled with chlorine gas for 10 minutes, and stirred for an additional 30-45 minutes. The reaction mixture was poured into ice water (200 g), stirred for 30 minutes, and extracted with dichloromethane (2 X 100 mL). The combined dichloromethane extracts were cooled in an ice bath to approximately 5°C and concentrated. Aqueous ammonium hydroxide (40 mL) was added slowly resulting in foaming and bubbling as the ammonia was added. After 30 minutes, the bubbling subsided, and the organic layer was separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic extracts were washed with 1N phosphoric acid (50 mL), brine, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give the title compound as a white solid (3.85 g). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.28 (s, 2 H) 7.44 (m, 6 H) 7.63 (d, *J*=2.94 Hz, 1 H) 7.79 (s, 2 H) 8.01 (d, *J*=8.82 Hz, 1 H). ESI m/z (M+H)⁺ 309.

Example 304D

2-amino-5-(benzyloxy)benzenesulfonamide

The product of Example 304C (3.85 g, 0.0125 mol) was treated with iron powder (4.3 g, 0.077 mol, 6.15 equivalent) and ammonium chloride (4.4 g, 0.082 mol) in methanol (100 mL) and water (50 mL), and stirred at reflux for 1 hour. The hot reaction mixture was filtered through fluted filter paper and washed with hot methanol. The filtrate was concentrated under reduced pressure to a white semi-solid that was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give the title compound as a off white solid (2.5 g). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.98 (s, 2 H) 5.46 (s, 2 H) 6.76 (d, *J*=8.82 Hz, 1 H) 7.01 (dd, *J*=8.82, 2.94 Hz, 1 H) 7.21 (d, *J*=2.94 Hz, 1 H) 7.23 (s, 2 H) 7.37 (m, 5 H). ESI m/z (M+H)⁺ 279. ESI m/z (M-H)⁻ 277.

Example 304E1-amino-N-[2-(aminosulfonyl)-4-(benzyloxy)phenyl]-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide

The products of Example 304D (4.0g, 14.37 mmol) and Example 226C (2.42 g, 7.20 mmol) in toluene (50 mL) were reacted at 118°C for 4 hours. The mixture was filtered while still warm and the solid dried to yield the title compound (3.13 g, 90%). MS (ESI-) m/z 479 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.20 (s, 2 H) 5.76 (s, 2 H) 7.40 (m, 10 H) 7.84 (m, 2 H) 8.02 (d, J=8.46 Hz, 1 H) 8.10 (dd, J=8.09, 1.47 Hz, 1 H) 12.31 (s, 1 H) 16.41 (s, 1 H).

Example 304F1-amino-3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one

The product of Example 304E (3.13 g, 6.51 mmol) was suspended in 10% potassium hydroxide solution (50 mL), heated at 125°C for 24 hours then at 140°C for 24 hours. The mixture was poured into ice and 1 M hydrochloric acid, filtered, and dried to give the title compound (2.03 g, 67%). MS (ESI-) m/z 461 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.18 (s, 2 H) 5.33 (s, 2 H) 7.06 (m, 1 H) 7.25 (m, 3 H) 7.43 (m, 6 H) 7.69 (d, J=7.72 Hz, 1 H) 8.06 (d, J=8.09 Hz, 1 H) 16.31 (s, 1 H).

Example 304G3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclobutylideneamino)-4-hydroxyquinolin-2(1H)-one

The product of Example 304F (0.285 g, 0.62 mmol) in N,N-dimethylacetamide (1.5 mL) was reacted with cyclobutanone (0.85 mL, 10.9 mmol) in a sealed tube in a microwave reactor at 130°C for 45 minutes. The reaction was cooled to 25°C, concentrated under a stream of nitrogen warmed through a manifold heated to 165°C and the resulting residue was triturated with diethyl ether to give the title compound (0.178g, 56%).

Example 304H3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclobutylamino)-4-hydroxyquinolin-2(1H)-one

The product of Example 304G (0.178 g, 0.35 mmol) in tetrahydrofuran (3 mL) at 0°C was treated with methanol (0.025 mL, 0.70 mmol), followed by dropwise addition of a 2.0 M solution of lithium borohydride in tetrahydrofuran (0.260 mL, 0.52 mmol), stirred at 25°C for one hour, and diluted with 1 N HCl. The resulting precipitate was filtered and dried. The solid was dissolved in tetrahydrofuran and absorbed onto silica gel by evaporating to dryness.

The resulting silica was loaded onto a 2g Alltech sep pack and eluted with dichloromethane to give the title compound (0.059 g, 33%). MS (ESI-) m/z 515 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.55 (m, 1 H) 1.71 (m, 1 H) 2.04 (m, 4 H) 3.77 (m, 1 H) 5.26 (s, 2 H) 6.57 (d, J=5.15 Hz, 1 H) 7.45 (m, 8 H) 7.64 (d, J=9.56 Hz, 1 H) 7.88 (m, 1 H) 8.05 (d, J=8.46 Hz, 1 H) 8.17 (m, 1 H).

Example 304I

1-(cyclobutylamino)-4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

The product of Example 304H (0.059 g, 0.11 mmol) in tetrahydrofuran (4 mL) was reacted with platinum oxide (50 mg) under hydrogen atmosphere at 25°C for 20 hours. The catalyst was filtered off and the filtrate evaporated to give the title compound (0.048 g, 100%). MS (ESI-) m/z 425 (M-H)⁻.

Example 304J

2-({3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 304I (0.048 g, 0.11 mmol) in N,N-dimethylformamide (2 mL) was reacted with cesium carbonate (0.15 g, 0.45 mmol), bromoacetamide (0.026 mL, 0.18 mmol), and a catalytic amount of tetrabutylammonium iodide at 25°C for 3 hours. The reaction was concentrated under a stream of nitrogen stream of nitrogen warmed through a manifold heated to 165°C and the resulting residue was triturated with water, filtered and dried. The resulting solid was triturated in hot ethyl acetate, filtered, and dried to give the title compound (0.020 g, 37%). MS (ESI-) m/z 482 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.59 (m, 2 H) 1.99 (m, 4 H) 3.60 (m, 1 H) 4.49 (s, 2 H) 6.08 (d, J=6.62 Hz, 1 H) 7.05 (t, J=7.17 Hz, 1 H) 7.20 (m, 3 H) 7.40 (s, 1 H) 7.50 (m, 1 H) 7.65 (m, 2 H) 8.05 (d, J=7.72 Hz, 1 H) 16.25 (s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.59 (m, 1 H) 1.99 (m, 4 H) 3.61 (m, 2 H) 4.49 (s, 2 H) 6.08 (d, J=6.62 Hz, 1 H) 7.05 (m, 1 H) 7.21 (m, 2 H) 7.40 (s, 2 H) 7.50 (m, 1 H) 7.64 (m, 2 H) 8.06 (dd, J=7.91, 1.29 Hz, 1 H) 8.32 (s, 1 H).

Example 305A

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclopentylideneamino)-4-

hydroxyquinolin-2(1H)-one

The product of Example 304F (0.284 g, 0.61 mmol) and cyclopentanone (0.80 mL, 9.04 mmol) in N,N-dimethylacetamide (2 mL) were reacted at 130°C for 40 minutes in a microwave reactor in a sealed tube. The reaction was concentrated under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.210 g, 65%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.72 (m, 2 H) 1.87 (m, 2 H) 2.16 (m, 2 H) 2.71 (m, 2 H) 5.18 (s, 2 H) 7.31 (m, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 16.22 (s, 1 H).

Example 305B3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclopentylamino)-4-hydroxyquinolin-2(1H)-one

The produce of Example 305A (0.21 g, 0.40 mmol) in tetrahydrofuran (3 mL) and methanol (0.030 mL) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 0.30 mL, 0.60 mmol). The reaction was stirred at 25°C for 1 hour then diluted with 1 M aqueous hydrochloric acid and filtered. The product was purified by dissolving in tetrahydrofuran, absorbing onto silica gel, loading onto a 2g Alltech Sep-pack and eluting with dicholomethane. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.124 g, 59%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.54 (m, 4 H) 1.79 (m, 2 H) 2.55 (m, 2 H) 3.94 (m, 1 H) 5.26 (s, 2 H) 6.23 (m, J=6.99, 4.04 Hz, 1 H) 7.43 (m, 8 H) 7.69 (d, J=6.99 Hz, 1 H) 7.87 (m, 1 H) 8.09 (d, J=8.09 Hz, 1 H) 8.16 (d, J=6.62 Hz, 1 H) 14.08 (s, 1 H) 15.18 (s, 1 H).

Example 305C1-(cyclopentylamino)-4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

The product of Example 305B (0.122 g, 0.23 mmol) in tetrahydrofuran (15 mL) was reacted with a catalytic amount of palladium hydroxide on carbon, a catalytic amount of 5% palladium on carbon, and ammonium formate (0.080 g, 1.27 mmol) at 60°C for 2 hours. The warm reaction mixture was filtered through celite and the filtrate was evaporated under reduced pressure to give the title compound (0.10g, 100%). MS (ESI-) m/z 439 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.54 (m, 4 H) 1.78 (m, J=2.94 Hz, 2 H) 2.58 (m, 2 H) 3.91 (m, 1 H) 6.25 (m, 1 H) 7.13 (m, 2 H) 7.45 (m, 1 H) 7.54 (d, J=9.19 Hz, 1 H) 7.85 (m, 1 H) 8.12 (m, 2 H) 10.45 (s, 1 H) 14.00 (s, 1 H) 15.25 (s, 1 H).

Example 305D2-({3-[1-(cyclopentylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-

1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 305C (0.10 g, 0.23 mmol) was reacted with cesium carbonate (0.30 g, 0.92 mmol), 2-bromoacetamide (0.050 g, 0.37 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (5 mL) at 25°C for 2 hours. The reaction was concentrated to half the volume under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting solution was diluted with water and the precipitate was collected by filtration and dried to give the title compound (0.095 g, 85%). MS (ESI⁺) m/z 496 (M-H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.52 (m, 6 H) 1.76 (m, 2 H) 3.70 (m, 1 H) 4.47 (s, 2 H) 5.68 (d, J=4.88 Hz, 1 H) 7.03 (t, J=7.63 Hz, 1 H) 7.20 (m, 5 H) 7.46 (t, J=7.32 Hz, 1 H) 7.70 (d, J=8.54 Hz, 1 H) 8.06 (d, J=7.32 Hz, 1 H) 16.15 (s, 1 H).

Example 306A3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclohexylideneamino)-4-hydroxyquinolin-2(1H)-one

The title compound was prepared according to the procedure as described in Example 304G, substituting cyclohexanone for cyclobutanone.

Example 306B3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(cyclohexylamino)-4-hydroxyquinolin-2(1H)-one

The title compound was prepared according to the procedure described in Example 304H, substituting the product of Example 306A for the product of Example 304G (0.11 g, 78%).

Example 306C1-(cyclohexylamino)-4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

The title compound was prepared according to the procedure of Example 305C substituting the product of Example 306B for the product of Example 305B (39 mg, 42%).

Example 306D2-({3-[1-(cyclohexylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 306C (13 mg, 0.028 mmol) in N,N-dimethylformamide (5 mL) was reacted with cesium carbonate (0.0137g, 0.114 mol) and 2-bromoacetamide (0.008g, 0.058mmol) according to the procedure as described in Example 304J to give the title compound. The sodium salt was prepared according to the procedure of Example 1D (7 mg, 48%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.36 (m, 10 H) 2.96 (bs, 1 H) 4.49 (s, 2 H) 5.67 (d, J=4.04 Hz, 1 H) 7.04 (t, J=7.54 Hz, 1 H) 7.20 (m, 3 H) 7.40 (s, 1 H) 7.47 (m, 1 H) 7.62 (s, 1 H) 7.74 (d, J=8.46 Hz, 1 H) 8.05 (d, J=6.62 Hz, 1 H) 16.26 (s, 1 H). (ESI-) m/z 510 (M-H)⁻, m/z 532 (M+Na-H)⁻.

Example 307

4-[(2-chloro-1,3-thiazol-5-yl)methyl]-7-hydroxy-6-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)thieno[3,2-b]pyridin-5(4H)-one

Example 307A

Ethyl [7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]acetate

The title compound was prepared according to the procedure of Example 1C substituting the product of Example 304D for 2-amino-benzenesulfonamide.

Example 307B

Ethyl (7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

The product of Example 307A (1.42 g, 3.79 mmol) in tetrahydrofuran (60 mL) was reacted with 10% palladium on carbon (0.2 g) under hydrogen atmosphere for 16 hours at 25°C. The reaction mixture was filtered and concentrated under reduced pressure to an oil. The residue was purified on silica gel eluting with ethyl acetate to give the title compound as of a white solid (0.8 g).

Example 307C

Ethyl {1,1-dioxido-7-[(triisopropylsilyl)oxy]-4H-1,2,4-benzothiadiazin-3-yl}acetate

The product of Example 307B (0.1 g, 0.352 mmol) was reacted with 2,6-lutidine (0.045 mL, 0.387 mmol) and triisopropyl trifluoromethanesulfonate (0.1 mL, 0.387 mmol) in dichloromethane (10 mL) at 5°C for 3 hours. The reaction was diluted with dichloromethane and extracted with aqueous 1N phosphoric acid. The organic layer was washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound as a light yellow solid (0.13 g, 84%).

Example 307D

4-[(2-Chloro-1,3-thiazol-5-yl)methyl]-6-{1,1-dioxido-7-[(triisopropylsilyl)oxy]-4H-1,2,4-

benzothiadiazin-3-yl}-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one

The title compound was prepared according to the procedure of Example 1D substituting the product of Example 140A for the product of Example 1B and substituting the product of Example 307C for the product of Example 1C (0.29 g, 66%). MS (ESI-) *m/z* 649 (M-H)⁻. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 1.09 (d, *J*=7.35 Hz, 18 H) 1.28 (m, 3 H) 5.63 (s, 2 H) 7.22 (d, *J*=2.57 Hz, 1 H) 7.31 (dd, *J*=8.82, 2.94 Hz, 1 H) 7.65 (d, *J*=8.82 Hz, 1 H) 7.86 (d, *J*=5.52 Hz, 1 H) 7.95 (s, 1 H) 8.42 (d, *J*=5.52 Hz, 1 H) 14.05 (s, 1 H) 14.96 (s, 1 H).

Example 307E

4-[(2-chloro-1,3-thiazol-5-yl)methyl]-7-hydroxy-6-(7-hydroxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)thieno[3,2-*b*]pyridin-5(4*H*)-one

The product of Example 307D (0.235g 0.36mmol.) in tetrahydrofuran (10mL) was reacted with tetrabutylammonium fluoride in tetrahydrofuran (1M, 0.43mL) at 25°C for 2 hours. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with 1 M HCl and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound (0.15g, 84%). MS (ESI-) *m/z* 493 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 5.63 (s, 2 H) 7.17 (s, 1 H) 7.20 (d, *J*=2.57 Hz, 1 H) 7.57 (d, *J*=8.82 Hz, 1 H) 7.85 (d, *J*=5.52 Hz, 1 H) 7.95 (s, 1 H) 8.42 (d, *J*=5.15 Hz, 1 H) 10.42 (s, 1 H) 13.95 (s, 1 H) 15.10 (s, 1 H).

Example 308

2-[(3-{4-[(2-chloro-1,3-thiazol-5-yl)methyl]-7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl}-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl)oxy]acetamide

The product of Example 307E (0.065g, 0.13 mmol.) in *N,N*-dimethylformamide (5 mL) was reacted with cesium carbonate (0.171g, 0.53 mmol) and 2-bromoacetamide (0.036g, 0.26 mmol) at 25°C for 24 hrs. The reaction mixture was diluted with water and the resulting precipitate was collected by filtration to give the title compound (0.036 g, 50%). MS (ESI-) *m/z* 550 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 4.60 (s, 2 H) 5.63 (s, 2 H) 7.38 (t, *J*=2.21 Hz, 1 H) 7.42 (d, *J*=2.94 Hz, 1 H) 7.44 (s, 1 H) 7.69 (d, *J*=8.46 Hz, 1 H) 7.66 (s, 1 H) 7.85 (d, *J*=5.52 Hz, 1 H) 7.95 (s, 1 H) 8.42 (d, *J*=5.52 Hz, 1 H) 14.04 (s, 1 H) 14.99 (s, 1 H).

Example 309A1-Benzyl-4-hydroxy-1H-quinolin-2-one

The title compound was prepared according to the procedure as described in D. R. Buckle, B. C. Cantello, H. Smith, B. A. Spicer, *Journal of Medicinal Chemistry*, **18**, 726-732 (1975).

Example 309B1-Benzyl-3-(bis-methylsulfanyl-methylene)-1H-quinoline-2,4-dione

A suspension of sodium hydride (0.75 g, 16 mmol.) in N,N-dimethylformamide (20 mL) at 0°C was added a solution of the product of Example 309A (2 g, 7.97 mmol) in N,N-dimethylformamide (30 mL) over 30 minutes. The red-orange mixture was warmed to 25°C and stirred for 30 minutes as a violet color developed. The reaction was then heated at 50°C for 2 hours and cooled to 25°C over 30 minutes. Carbon disulfide (1.13 mL, 16 mmol) was added to the mixture. The mixture was heated at 50°C for 2 hrs (red-brown color developed) and cooled to 25°C. Methyl iodide (1.2 mL, 16 mmol) was added and the reaction was stirred at 25°C for 30 minutes. The reaction was quenched with phosphate buffer (10 mL, pH = 7) and the reaction was concentrated under reduced pressure. The residue was triturated with pH 7 phosphate buffer and ethyl acetate/hexanes (1:1), the resulting orange solids were collected by filtration, washed with hexanes and dried under reduced pressure to give the title compound (1.76 g, 62%). ¹H NMR (300 MHz, CDCl₃) δ ppm 2.65 (s, 6 H) 5.43 (s, 2 H) 7.06 (d, J=8.46 Hz, 1 H) 7.14 (m, 1 H) 7.28 (m, 5 H) 7.43 (m, 1 H) 8.24 (dd, J=7.72, 1.47 Hz, 1 H).

Example 309Cmethyl 4-(benzylthio)-5-nitrothiophene-3-carboxylate

The title compound was prepared according to the procedure as described in Stanetty, P. et. al., *Journal of Heterocyclic Chemistry*, **36**, 761-765 (1999).

Example 309D[4-(benzylthio)-5-nitrothien-3-yl]methanol

The product of Example 309C (5g, 16.2 mmol) in dichloromethane (150 mL) at -40°C was reacted with diisobutylaluminum hydride (1 M in dichloromethane, 36 mL, 2.2 equivalents) added dropwise. The reaction was stirred for 15 minutes after complete addition, quenched with 10% aqueous sodium potassium tartrate solution and stirred at 25°C for 1 hour. The organic layer was separated, filtered through celite[®] (diatomaceous earth) and the filtrate was concentrated under reduced pressure. The resulting oil was purified by

flash chromatography on silica gel with a Biotage-40s column eluting with 2:98 methanol/dichloromethane to give the title compound as an oil, (4.32 g, 95%). ¹H NMR (300 MHz, CDCl₃) δ ppm 4.21 (s, 2 H), 4.39 (s, 2 H), 7.11 (m, 3 H), 7.23 (m, 2 H) 7.40 (s, 1 H).

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Example 309E3-(benzylthio)-4-[(methoxymethoxy)methyl]-2-nitrothiophene

The product of Example 309D (3.9g, 13.9 mmol) in dichloromethane (8 mL) was reacted with diisopropylethylamine (7.42 mL, 3 equivalents) and methoxymethyl chloride (2.38 mL, 2.25 equivalents) at 25°C 16 hours. The reaction was concentrated under reduced
10 pressure and the residue purified by flash chromatography on silica gel using a Biotage-40m column eluting with dichloromethane to give the title compound as a yellowish oil, (4.32 g, 94%). ¹H NMR (300 MHz, CDCl₃) δ ppm 3.36 (s, 3 H), 4.20 (s, 2 H), 4.34 (s, 2 H), 4.62 (s, 2 H), 7.13 (m, 3 H), 7.21 (m, 2 H), 7.40 (s, 1 H).

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Example 309F4-[(methoxymethoxy)methyl]-2-nitrothiophene-3-sulfonamide

The product of Example 309E (4g, 12.3 mmol) in dichloromethane (70 mL) and 1 N aqueous hydrochloric acid (35mL) at 0°C was reacted with chlorine gas bubbled in slowly over a period of 0.5 hour, then stirred for an additional 1 hour. The reaction mixture was
20 purged with nitrogen gas to remove excess chlorine and treated with solid sodium bisulfite (11 g) added slowly to the mixture with stirring for 5 minutes. Dichloromethane (15 mL) and water (15 mL) were added, the organic layer was separated and eluted through 40g of 50:50 mixture of MgSO₄/Na₂SO₄. The filtrate was concentrated under reduced pressure. A solution of the concentrate (4.7 g) in dichloromethane (100 mL) at -40°C was bubbled with
25 ammonia gas over a period of 10 minutes. The reaction mixture was stirred for an additional 15 minutes, purged with nitrogen gas to dispel the excess ammonia and concentrated under reduced pressure. The concentrate was purified by flash chromatography on silica gel using a Biotage-40s column eluting with 5:95 methanol/ dichloromethane to give the title
30 compound as an oil (2.3 g, 66%). ¹H NMR (300 MHz, CDCl₃) δ ppm 3.31 (m, 3 H), 4.70 (s, 2 H), 4.73 (s, 2 H), 7.85 (m, 2 H), 7.88 (s, 1 H).

Example 309G2-amino-4-[(methoxymethoxy)methyl]thiophene-3-sulfonamide

The product of Example 309F (1.8 g, 6.4 mmol) was reacted with iron powder (1.43
35 g, 4 equivalents) in acetic acid (70 mL) at 50°C for 7.5 hours then concentrated under reduced pressure. A slurry of the residue in 5% methanol/dichloromethane (60mL) and water (6 mL) was filtered through silica gel (20 g) and further rinsed with 5%

methanol/dichloromethane (300mL). The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel using a Biotage-12s column eluting with 2.5:97.5 methanol: dichloromethane to give the title compound (1g, 62%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.30 (s, 3 H), 4.53 (s, 2 H), 4.66 (s, 2 H), 6.28 (s, 1 H), 6.61 (s, 2 H), 6.94 (s, 2 H).

Example 309H

1-Benzyl-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl}quinolin-2(1H)-one

The product of Example 309G (35 mg, 0.14 mmol) and the product of Example 309B (50 mg, 0.14 mmol) were reacted in toluene (3 mL) at 100°C for 3 hours. The resulting precipitate was collected by filtration and washed with toluene and diethyl ether to give the title compound (52 mg, 73.3%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.26 (s, 3 H), 4.65 (s, 2 H), 4.72 (s, 2 H), 5.62 (s, 2 H), 7.28 (m, 7 H), 7.43 (s, 2 H), 7.51 (d, J=8.09 Hz, 1 H), 7.75 (m, 1 H), 8.22 (d, J=8.09 Hz, 1 H).

Example 310

1-Benzyl-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]quinolin-2(1H)-one

A suspension of the product of Example 309H (46 mg, 0.09 mmol) in 6N aqueous hydrochloric acid (2.5 mL) and tetrahydrofuran (5 mL) was heated at 70°C for 4 hours, cooled to 25°C and let stand for 18 hours at room temperature. The resulting precipitate was collected by filtration and washed with water and diethyl ether to give the title compound (39 mg, 92.8%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 4.63 (s, 2 H), 5.62 (s, 2 H), 7.31 (m, 6 H), 7.41 (t, J=7.72 Hz, 1 H), 7.53 (d, J=8.46 Hz, 1 H), 7.76 (t, J=7.91 Hz, 1 H), 8.22 (dd, J=8.09, 1.47 Hz, 1 H).

Example 311A

N-(tert-butyl)-5-chlorothiophene-2-sulfonamide

The title compound was prepared according to the procedure as described in Unterhalt, B, Moghaddam, S. *Pharmazie*, **1994**, 49, 115-117.

Example 311B

3-azido-N-(tert-butyl)-5-chlorothiophene-2-sulfonamide

A solution of Example 311A (1.01 g, 3.99 mmol) in tetrahydrofuran (32 mL) at -78°C

was treated with dropwise addition of sec-BuLi (1.4 M in hexane, 2.1 equivalents). The reaction was warmed to -20°C and stirred for 30 minutes, treated with a solution of tosyl azide (1.1 equivalent) in tetrahydrofuran (7 mL) at -20°C, stirred at 25°C for 18 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 30% dichloromethane in hexane to 100% dichloromethane to give approximately a 2:1 mixture of starting material to the title compound.

Example 311C

3-Amino-5-chloro-N-isopropylthiophene-2-sulfonamide

A solution of the product of Example 311B (0.739 g) in toluene (20 mL) and hexadecyltributylphosphonium bromide (0.128 g, 0.25 mmol) at 0°C was treated dropwise with a solution of sodium borohydride (0.109 g, 2.9 mmol) in water (0.80 mL). The reaction was stirred at 25°C for 18 hours and at 5 °C for 72 hours. The reaction was extracted with ethyl acetate. The organic layer was washed with 1N aqueous sodium hydroxide, water, and brine and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with a gradient of 1:1 hexanes/dichloromethane to 100 % dichloromethane to give the title compound (0.252 g, 23%). ¹H NMR (300 MHz, CDCl₃) δ ppm 6.36 (s, 1 H) 4.93 (br s, 2 H) 4.60 (br s, 1 H) 1.30 (s, 9 H).

Example 311D

3-Amino-5-chloro-N-isopropylthiophene-2-sulfonamide, trifluoroacetate salt

The product of Example 311C (0.0998 g) in trifluoroacetic acid (3.9 mL) was stirred at 25°C for 18 hours. The reaction was concentrated under reduced pressure and azeotroped three times with ethyl acetate to give the title compound as a trifluoroacetate salt (0.160 g). ¹H NMR (300 MHz, CDCl₃) δ ppm 6.41 (s, 1 H) 5.22 (br s, 2 H) 4.84 (br s, 2 H).

Example 311E

1-Benzyl-3-(6-chloro-1,1-dioxido-4H-thieno[3,2-e][1,2,4]thiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

The title compound was prepared according to the procedure of Example 309H, substituting the product of Example 311D for the product of Example 309G, in the presence of diisopropylethylamine (3 equivalents). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 16.97 (s, 1 H) 8.11 (d, J=8.09 Hz, 1 H) 7.20 (m, 9 H) 5.40 (s, 2 H).

Example 312A5-Bromo-4-nitro-1H-imidazole

5 4-Bromo-1H-imidazole (2.0 g, 13.6 mmol) was reacted with concentrated nitric acid (0.947 mL, 14.96 mmol) in concentrated sulfuric acid (20 mL) at 110 °C for 1 hour. The reaction was cooled to 25°C and poured into 200 mL of ice water. The resulting white precipitate formed was collected by filtration to give the title compound (2.3 g, 87%). MS (ESI-) m/z 191 (M-H)-. 1H NMR (300 MHz, DMSO-d₆) δ ppm 7.99 (s, 1H).

Example 312B1-Benzyl-5-bromo-4-nitro-1H-imidazole

15 A solution of the product of Example 312A (2.3 g, 11.98 mmol) in anhydrous N,N-dimethylformamide (40 mL) at 25°C was reacted with sodium bicarbonate (2.0 g, 24 mmol) and dropwise addition of benzyl bromide (1.58 mL, 13.17 mmol). The reaction was stirred for an additional 12 hours at 25°C. The reaction was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase column chromatography on a C18 column, eluting with a gradient of
20 acetonitrile in water containing 0.1% trifluoroacetic acid (5:95 to 100) to give the title compound (1.63 g, 48%). MS (ESI+) m/z 284 (M+H)⁺. 1H NMR (300 MHz, DMSO-d₆) δ ppm 5.38 (s, 2H), 7.24-7.42 (m, 5H), 8.28 (s, 1H).

Example 312Cammonium 1-benzyl-4-nitro-1H-imidazole-5-thiolate

25 A solution of the product of Example 312B in 5N ammonium hydroxide (16 mL) and dioxane (10 mL) at 35° C was bubbled with hydrogen sulfide gas for 15 minutes. The reaction flask was then sealed and stirring was continued for 1 hour. The reaction was purged with nitrogen gas for 10 minutes and concentrated under reduced pressure to give the
30 title compound.

Example 312D1-benzyl-4-nitro-1H-imidazole-5-sulfonyl chloride

35 A solution of the product of Example 312C in 1N HCl (20 mL) and dioxane (10 mL) at 30° C was bubbled with chlorine gas for 15 minutes. The reaction flask was sealed and the reaction mixture stirred for 1 hour. The chlorine addition was repeated as above and the reaction mixture stirred for an additional 1 hour. The reaction was cooled in an ice bath.

Cold water was added to the reaction and the resulting precipitate was collected by filtration to give the title compound (1.51 g, 87% for 2 steps). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.57 (s, 2H), 7.27-7.40 (m, 5H), 7.74 (s, 1H).

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Example 312E1-benzyl-4-nitro-1H-imidazole-5-sulfonamide

A solution of the product of Example 312D (1.5 g, 4.97 mmol) in dioxane (25 mL) at 25°C was bubbled with ammonia gas for 10 minutes. The reaction flask was sealed and the reaction mixture was stirred an additional 30 minutes. This above process was repeated. The reaction mixture was concentrated under reduced pressure and the residue was washed with cold water several times to give the title compound (1.27 g, 90%). MS (ESI-) m/z 281 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.61 (s, 2H), 7.26-7.42 (m, 5H), 8.17 (s, 1H).

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Example 312F4-amino-1-benzyl-1H-imidazole-5-sulfonamide

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A solution of the product of Example 312E (434 mg, 1.54 mmol) in acetic acid (4.3 mL) and dioxane (4.3 mL) was reacted with iron powder (343 mg, 6.15 mmol) at 50°C for 3 hours. The reaction mixture was cooled to 25°C, filtered through a pad of celite® (diatomaceous earth) and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (2x) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel using a gradient of methanol in dichloromethane (0-5%) to give the title compound (180 mg, 46%). MS (ESI+) m/z 253 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.24 (s, 2H), 7.22-7.39 (m, 5H), 7.43 (s, 1H).

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Example 312G1-benzyl-3-(7-benzyl-1,1-dioxido-4,7-dihydroimidazo[4,5-e][1,2,4]thiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one

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The product of Example 312F (152 mg, 0.602 mmol) was reacted with the product of Example 309B (214 mg, 0.602 mmol) in toluene (8 mL) at 100°C for 3 hours. The reaction was allowed to cool to 25°C and diluted with hexanes. The resulting precipitate was collected by filtration. The residue was chromatographed on silica gel, eluting with gradient of 0 – 2% methanol in dichloromethane to give the title compound (155 mg, 50%). MS (ESI+) m/z 512 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.42 (s, 2H), 5.63 (s, 2H), 7.22-7.44 (m, 11H), 7.53-7.56 (m, 1H), 7.74-7.79 (m, 1H), 8.20-8.23 (dd, J=8.1, 1.5 Hz, 1H),

35

8.32 (s, 1H).

Example 313

5 1-benzyl-3-(1,1-dioxido-4,7-dihydroimidazo[4,5-e][1,2,4]thiadiazin-3-yl)-4-
 hydroxyquinolin-2(1H)-one

10 The product of Example 312 (19.35 mg, 0.0378 mmol) in anhydrous dimethyl sulfoxide (2.5 mL) was reacted with a solution of potassium *tert*-butoxide in tetrahydrofuran (1M, 0.265 mL, 0.265 mmol) at 25°C for 12 hours. The reaction was quenched by adding
15 saturated aqueous ammonium chloride solution and extracted with dichloromethane. The aqueous layer was made basic with a sodium bicarbonate solution and extracted twice with dichloromethane. The combined organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed
on a reverse phase C18 column eluting with 5% – 100% acetonitrile in water containing 0.1%
trifluoroacetic acid to give the title compound (17 mg, 81%). MS (ESI-) *m/z* 420 (M-H)⁻.
1H NMR (300 MHz, DMSO-d₆)/CF₃COOD) δ ppm 5.6 (s, 2H), 7.17-7.27 (m, 5H), 7.35-7.40 (t, J=7.64 Hz, 1H), 7.51-7.63 (d, J=8.3 Hz, 1H), 7.69-7.73 (t, J=8.8 Hz, 1H), 8.0-8.01 (m, 1H), 8.18-8.20 (dd, J=8.3, 1.2 Hz, 1H).

Example 314

20 N²-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-
 4H-1,2,4-benzothiadiazin-7-yl}glycinamide

A solution of the product of Example 206 (10.8 mg, 0.023 mmol) in concentrated sulfuric acid (0.6 mL) was treated with a slow addition of water (0.1 mL) and the yellow
25 solution was stirred at 25°C for 18 hours. The reaction mixture was poured onto ice, the pH was adjusted to pH 9 with 50% NaOH and aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water, brine, dried over magnesium sulfate and filtered. The filtrate
concentrated under reduced pressure to give the title compound as a yellow solid (9.1 mg,
30 83%). MS (ESI-) *m/z* 483 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d, J=6.62 Hz, 6 H) 1.49 (m, 2 H) 1.64 (m, 1 H) 3.63 (d, J=5.52 Hz, 2 H) 4.30 (m, 2 H) 6.23 (br s, 1 H) 6.69 (s, 1 H) 6.87 (d, J=7.35 Hz, 1 H) 7.12 (s, 3 H) 7.42 (s, 1 H) 8.36 (d, J=7.35 Hz, 1 H) 8.52 (s, 1 H) 15.62 (br s, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.96 (d,
35 J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 3.62 (d, J=5.88 Hz, 2 H) 4.29 (m, 2 H) 6.20 (m, 1 H) 6.68 (d, J=2.57 Hz, 1 H) 6.86 (m, 1 H) 7.41 (m, 3 H) 8.35 (dd, J=7.72, 1.84 Hz, 1 H) 8.50 (dd, J=4.78, 1.84 Hz, 1 H) 15.63 (s, 1 H).

Example 315A

1-butyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-one

A slurry of the product of Example 89A (3.24 g, 11.16 mmol) in 2 N sodium hydroxide (100 mL) was heated at reflux for 3 hours, cooled to 10°C and treated dropwise with concentrated hydrochloric acid to a constant pH of 3. The resulting white solid was collected by filtration, washed with water and dried to give the title compound (2.47 g, quantitative). MS (APCI+) m/z 219 (M+H)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 0.90 (t, *J*=7.35 Hz, 3 H) 1.32 (m, 2 H) 1.57 (m, 2 H) 4.31 (m, 2 H) 5.89 (s, 1 H) 7.27 (dd, *J*=7.72, 4.78 Hz, 1 H) 8.23 (dd, *J*=7.72, 1.84 Hz, 1 H) 8.64 (dd, *J*=4.78, 1.84 Hz, 1 H) 11.61 (s, 1 H).

Example 315B

3-[bis(methylthio)methylene]-1-butyl-1,8-naphthyridine-2,4(1*H*,3*H*)-dione

The title compound was prepared according to the procedure of Example 309B substituting the product of Example 315A for the product of Example 309A. ¹H NMR (300 MHz, CDCl₃) δ ppm 0.97 (t, *J*=7.35 Hz, 3 H) 1.44 (dd, *J*=15.44, 7.35 Hz, 2 H) 1.69 (m, 2 H) 2.64 (s, 6 H) 4.39 (m, 2 H) 7.10 (dd, *J*=7.72, 4.78 Hz, 1 H) 8.45 (dd, *J*=7.72, 1.84 Hz, 1 H) 8.56 (dd, *J*=4.60, 2.02 Hz, 1 H).

Example 315C

1-butyl-4-hydroxy-3-[7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1,8-naphthyridin-2(1*H*)-one

The product of Example 309G (110 mg, 0.43 mmol) and the product of Example 315B (140.6 mg, 0.43 mmol) were reacted in toluene (5 mL) at 100°C for 3 hours. The reaction was concentrated under reduced pressure and the residue was purified by chromatography on silica gel using a Biotage-12m column eluting with 1:99 methanol:dichloromethane to give the title compound as a white solid (114 mg, 54.6%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, CDCl₃) δ, ppm 1.00 (t, J=7.35 Hz, 3 H), 1.46 (m, 2 H), 1.74 (m, 2 H), 3.45 (s, 3 H), 4.56 (m, 2 H), 4.80 (s, 2 H), 4.84 (s, 2 H), 7.09 (s, 1 H), 7.26 (s, 1 H), 7.36 (dd, J=8.09, 4.41 Hz, 1 H), 8.57 (dd, J=8.09, 1.84 Hz, 1 H), 8.81 (dd, J=4.78, 1.84 Hz, 1 H), 15.06 (s, 1 H), 15.11 (s, 1 H).

Example 316

1-butyl-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1,8-naphthyridin-2(1*H*)-one

The product of Example 315C (92 mg, 0.19 mmol) was reacted with 6N aqueous hydrochloric acid (4 mL) and tetrahydrofuran (8 mL) at 70°C for 3 hours. The reaction was concentrated under reduced pressure to remove the tetrahydrofuran, and treated with methanol (5 mL). The resulting precipitate was collected by filtration and washed with water and diethylether to give the title compound as a white solid (65 mg, 77.8%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, CDCl₃) δ ppm 1.00 (t, J=7.35 Hz, 3 H), 1.47 (dd, J=15.26, 7.54 Hz, 2 H), 1.73 (m, 2 H) 4.57 (m, 2 H), 4.86 (s, 2 H), 7.07 (s, 1 H), 7.37 (dd, J=8.09, 4.78 Hz, 1 H), 8.58 (dd, J=8.09, 1.84 Hz, 1 H), 8.82 (dd, J=4.60, 2.02 Hz, 1 H), 14.94 (s, 1 H), 15.24 (s, 1 H).

Example 317A

methyl 4-(aminosulfonyl)-5-nitrothiophene-3-carboxylate

A solution of the product of Example 309A (2g, 6.5 mmol) in dichloromethane (38 mL) and 1.5 N aqueous hydrochloric acid (21 mL) at 0°C was bubbled with chlorine gas over 30 minutes. The reaction flask was sealed and stirred for an additional 1 hour. Nitrogen gas was bubbled through the reaction to dispel the chlorine, followed by the addition of solid sodium bisulfite (5.12g) with stirring for 5 minutes. Dichloromethane (10 mL) and water (10 mL) were added to the reaction. The organic layer was separated and eluted through 20g of 1:1 mixture of magnesium sulfate and sodium sulfate. The filtrate was concentrated under reduced pressure, and the residue triturated with hexanes to give the sulfonyl chloride as a white solid (1.8 g, 97%). A solution of the crude sulfonyl chloride (1.5 g) in dichloromethane (15 mL) at -40°C was bubbled with ammonia gas over a period of 5 minutes. The reaction flask was sealed and stirred for another 15 minutes. Nitrogen gas was bubbled into the reaction mixture to dispel the ammonia. The reaction was concentrated under reduced pressure while maintaining the temperature under 0°C. The residue was chromatographed on silica gel using a Biotage-40s column eluting with 5:95 methanol:dichloromethane to give an oil. This oil was triturated with a mixture of 5% methanol:dichloromethane (20 mL) and hexanes (20 mL), to give the title compound as a yellow solid (0.75 g, 54%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.81 (s, 3 H), 7.88 (s, 2 H), 8.31 (s, 1 H).

methyl 5-amino-4-(aminosulfonyl)thiophene-3-carboxylate

The product of Example 317A (0.75 g, 2.86 mmol) was reacted with iron powder (0.64 g, 4 equivalents) in acetic acid (30 mL) at 50°C for 7.5 hours. The reaction was concentrated under reduced pressure and the residue was slurried in 5% methanol:dichloromethane (20mL) and water (2 mL) and filtered through a short column of silica gel (20 g) that was washed with 5% methanol:dichloromethane (200mL). The filtrate was concentrated under reduced pressure and residue was chromatographed on silica gel using a Biotage-12s column eluting with 1:1 ethyl acetate/ hexane to give the title compound as a yellow solid (0.527 g, 78%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.77 (s, 3 H), 6.84 (s, 2 H), 6.88 (s, 2 H), 7.28 (s, 1 H).

Example 317Cmethyl 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide

The product of Example 317B (180 mg, 0.76 mmol) and the product of Example 309B (270 mg, 0.76 mmol) were reacted in toluene (15 mL) at 100°C for 3 hours. The reaction was cooled to 25°C and the resulting precipitate was collected by filtration, washed with toluene and and diethyl ether to give the title compound (302 mg, 80%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 3.85 (s, 3 H), 5.61 (s, 2 H), 7.29 (m, 5 H), 7.40 (m, 1 H), 7.52 (m, 1 H), 7.74 (m, 1 H), 8.21 (d, J=7.72 Hz, 1 H), 8.26 (s, 1 H).

Example 3183-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxylic acid 1,1-dioxide

The product of Example 317C (90 mg, 0.09 mmol) was reacted with a solution of 1N aqueous sodium hydroxide (0.8 mL, 4.4 equivalents) in ethanol (2 mL) at 70°C for 1.5 hours. The reaction was filtered and the filtrate was acidified with 1N aqueous hydrochloric acid (0.8 mL). The resulting precipitate was collected by filtration and washed with water, methanol, and diethyl ether to give the title compound (80 mg, 91.5%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 5.62 (s, 2 H), 7.29 (m, 5 H), 7.42 (t, J=7.54 Hz, 1 H), 7.53 (d, J=8.82 Hz, 1 H), 7.76 (t, J=7.17 Hz, 1 H), 8.19 (s, 1 H), 8.22 (dd, J=8.09, 1.47 Hz, 1 H). The disodium salt of the title compound was prepared according to the procedure of Example 1D substituting two equivalent of sodium hydroxide for one equivalent of sodium hydroxide.

Example 319

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

The product of Example 317C (25 mg, 0.05 mmol) was suspended in ammonium hydroxide (1 mL) and heated at 40°C for 16 hours. The reaction mixture was cooled to 25°C, concentrated under reduced pressure to remove the excess ammonia, and a solution of 1N HCl (0.8 mL), MeOH (1 mL), and water (3 mL) was added to the reaction mixture. The resulting precipitate was collected by filtration and washed with water, methanol, and diethyl ether to give the title compound (19 mg, 78.4%). ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 5.62 (s, 2 H), 7.30 (m, 7 H), 7.41 (t, *J*=7.54 Hz, 1 H), 7.53 (m, 2 H), 7.76 (m, 2 H), 7.98 (s, 1 H), 8.22 (m, 1 H). The sodium salt of the title compound was prepared according to the procedure of Example 1D.

Example 320A

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-[[cyclopropylmethylene]amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 304F (0.800 g, 1.73 mmol) and cyclopropane carboxaldehyde (1.60 mL, 20.76 mmol) in N,N-dimethylacetamide (2 mL) were reacted at 120°C for 60 minutes in a microwave reactor in a sealed tube. The reaction was concentrated under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.750 g, 84%).

Example 320B

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

The produce of Example 320A (0.75 g, 1.46 mmol) in tetrahydrofuran (8 mL) and methanol (0.100 mL) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 1.0 mL, 2.0 mmol). The reaction was stirred at 25°C for 1 hour then diluted with 1 M aqueous hydrochloric acid and filtered. The product was purified by trituration with methyl sulfoxide, filtered and dried to give the title compound (0.296 g, 40%).

Example 320C

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

The product of Example 320B (0.296 g, 0.57 mmol) in tetrahydrofuran (15 mL) was reacted with a catalytic amount of palladium hydroxide on carbon, a catalytic amount of 5% palladium on carbon, and ammonium formate (0.180 g, 2.85 mmol) at 60°C for 2 hours. The warm reaction mixture was filtered through celite® (diatomaceous earth) and the filtrate was diluted with diethyl ether and the precipitate filtered and dried to give the title compound (0.127 g, 53%).

Example 320 D

2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetamide

The product of Example 320C (0.125 g, 0.29 mmol) was reacted with cesium carbonate (0.38 g, 1.17 mmol), 2-bromoacetamide (0.060 g, 0.43 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (3 mL) at 25°C for 2 hours. The reaction was concentrated to half the volume under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting solution was diluted with water and the precipitate was collected by filtration and dried to give the title compound (0.134 g, 95%). MS (ESI-) m/z 482 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.21 (m, J=3.86, 2.39 Hz, 2 H) 0.46 (m, 2 H) 0.99 (m, 1 H) 2.55 (m, 2 H) 4.49 (s, 2 H) 5.96 (t, J=6.43 Hz, 1 H) 7.06 (m, 1 H) 7.21 (m, 2 H) 7.40 (m, 2 H) 7.53 (m, 1 H) 7.62 (m, J=1.84 Hz, 1 H) 7.67 (d, J=8.46 Hz, 1 H) 8.07 (dd, J=8.09, 1.47 Hz, 1 H) 16.25 (s, 1 H).

Example 321A

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-[2-methylpropylidene]amino}quinolin-2(1H)-one

The product of Example 304F (0.150 g, 0.32 mmol) and isobutyraldehyde (0.44 mL, 4.84 mmol) in N,N-dimethylacetamide (1.5 mL) were reacted at 125°C for 40 minutes in a microwave reactor in a sealed tube. The reaction was concentrated under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.140 g, 84%).

Example 321B

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-

(isobutylamino)quinolin-2(1H)-one

The produce of Example 321A (0.140 g, 0.27 mmol) in tetrahydrofuran (3 mL) and methanol (0.020 mL) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 0.20 mL, 0.40 mmol). The reaction was stirred at 25°C for 1 hour then
5 diluted with 1 M aqueous hydrochloric acid and filtered. The product was purified by dissolving in tetrahydrofuran, absorbing onto silica gel, loading onto a silica gel column and eluting with dichloromethane. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.081 g, 58%).

Example 321C

4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-
(isobutylamino)quinolin-2(1H)-one

The product of Example 321B (0.081 g, 0.16 mmol) in tetrahydrofuran (10 mL) was reacted with a catalytic amount of palladium hydroxide on carbon, a catalytic amount of 5%
15 palladium on carbon, and ammonium formate (0.040 g, 0.64 mmol) at 60°C for 30 minutes. The warm reaction mixture was filtered through celite® (diatomaceous earth) and the filtrate was evaporated under reduced pressure to give the title compound (0.048 g, 72%).

Example 321D

2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-
benzothiadiazin-7-yl}oxy)acetamide

The product of Example 321C (0.048 g, 0.11 mmol) was reacted with cesium carbonate (0.11 g, 0.34 mmol), 2-bromoacetamide (0.023 g, 0.17 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (3 mL) at 25°C for 2
25 hours. The reaction was concentrated to half the volume under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting solution was diluted with water and the precipitate was collected by filtration and dried to give the title compound (0.042 g, 77%). MS (ESI-) m/z 484 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.03 (m, 6 H) 1.86 (m,
30 1 H) 3.25 (m, 2 H) 4.50 (m, 2 H) 5.94 (t, J=7.35 Hz, 1 H) 7.07 (t, J=7.72 Hz, 1 H) 7.21 (m, 2 H) 7.40 (s, 1 H) 7.58 (m, 2 H) 8.07 (dd, J=7.72, 1.47 Hz, 1 H) 16.23 (s, 1 H).

Example 322A

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-[butylideneamino]-4-

hydroxyquinolin-2(1H)-one

The product of Example 304F (0.150 g, 0.32 mmol) and butyraldehyde (0.29 mL, 3.24 mmol) in N,N-dimethylacetamide (1.5 mL) were reacted at 120°C for 25 minutes in a microwave reactor in a sealed tube. The reaction was concentrated under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.134 g, 80%).

Example 322B3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-(butylamino)-4-hydroxyquinolin-2(1H)-one

The produce of Example 322A (0.134 g, 0.26 mmol) in tetrahydrofuran (3 mL) and methanol (0.020 mL) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 0.195 mL, 0.39 mmol). The reaction was stirred at 25°C for 1 hour then diluted with 1 M aqueous hydrochloric acid and filtered. The product was purified by dissolving in tetrahydrofuran, absorbing onto silica gel, loading onto a silica gel column and eluting with dichloromethane. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.045 g, 33%).

Example 322C1-(butylamino)-4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

The product of Example 322B (0.045 g, 0.087 mmol) in tetrahydrofuran (8 mL) was reacted with a catalytic amount of palladium hydroxide on carbon, a catalytic amount of 5% palladium on carbon, and ammonium formate (0.03 g, 0.48 mmol) at 60°C for 4 hours. The warm reaction mixture was filtered through celite® (diatomaceous earth) and the filtrate was evaporated under reduced pressure to give the title compound (0.038 g, 100%).

Example 322D2-({3-[1-(butylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 322C (0.038 g, 0.089 mmol) was reacted with cesium carbonate (0.087 g, 0.27 mmol), 2-bromoacetamide (0.018 g, 0.13 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (3 mL) at 25°C for 2 hours. The reaction was concentrated to half the volume under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting solution was diluted with water and the precipitate was collected by filtration and dried to give the title compound (0.041 g, 95%). MS (ESI-) m/z 484 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.93 (t, J=7.17 Hz, 3

H) 1.48 (m, 4 H) 2.76 (m, 2 H) 4.49 (s, 2 H) 5.90 (t, J=6.80 Hz, 1 H) 7.06 (t, J=6.99 Hz, 1 H) 7.21 (m, 2 H) 7.40 (m, 1 H) 7.54 (m, 2 H) 8.07 (dd, J=8.09, 1.10 Hz, 1 H) 16.24 (s, 1 H).

5

Example 323A

3-[7-(benzyloxy)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-[(1*E*)-3-methylbutylidene]amino]quinolin-2(1*H*)-one

10

The product of Example 304F (0.220 g, 0.48 mmol) and isovaleraldehyde (0.77 mL, 7.18 mmol) in *N,N*-dimethylacetamide (1.5 mL) were reacted at 130°C for 35 minutes in a microwave reactor in a sealed tube. The reaction was concentrated under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting residue was triturated with diethyl ether and filtered to give the title compound (0.181 g, 72%).

15

Example 323B

3-[7-(benzyloxy)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-[(3-methylbutyl)amino]quinolin-2(1*H*)-one

20

The produce of Example 323A (0.061 g, 0.11 mmol) in tetrahydrofuran (3 mL) and methanol (0.010 mL) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 0.09 mL, 0.18 mmol). The reaction was stirred at 25°C for 1 hour then diluted with 1 M aqueous hydrochloric acid and filtered. The product was purified by dissolving in tetrahydrofuran, absorbing onto silica gel, loading onto a 2g Alltech Sep-pack and eluting with dichloromethane. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.037 g, 62%).

25

Example 323C

4-hydroxy-3-(7-hydroxy-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-[(3-methylbutyl)amino]quinolin-2(1*H*)-one

30

The product of Example 323B (0.037 g, 0.07 mmol) in tetrahydrofuran (8 mL) was reacted with a catalytic amount of palladium hydroxide on carbon, a catalytic amount of 5% palladium on carbon, and ammonium formate (0.018 g, 0.29 mmol) at 60°C for 30 minutes. The warm reaction mixture was filtered through celite® (diatomaceous earth) and the filtrate was evaporated under reduced pressure to give the title compound (0.025 g, 80%).

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Example 323D

2-[(3-{4-hydroxy-1-[(3-methylbutyl)amino]-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetamide

The product of Example 323C (0.025 g, 0.057 mmol) was reacted with cesium carbonate (0.055 g, 0.17 mmol), 2-bromoacetamide (0.012 g, 0.087 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (3 mL) at 25°C for 2 hours. The reaction was concentrated to half the volume under a stream of nitrogen warmed through a manifold heated to 165°C. The resulting solution was diluted with water and the precipitate was collected by filtration and dried to give the title compound (0.020 g, 72%). MS (ESI-) m/z 498 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.90 (m, 3 H) 1.33 (m, 6 H) 1.54 (m, 2 H) 4.49 (s, 2 H) 5.90 (m, 1 H) 7.06 (m, 1 H) 7.21 (m, 2 H) 7.40 (m, 1 H) 7.55 (m, 2 H) 8.07 (dd, J=8.27, 1.29 Hz, 1 H) 16.23 (s, 1 H).

Example 324A

4-amino-N-[2-(aminosulfonyl)-4-(benzyloxy)phenyl]-7-hydroxy-5-oxo-4,5-dihydrothienof[3,2-b]pyridine-6-carboxamide and N-[2-(aminosulfonyl)-4-(benzyloxy)phenyl]-7-hydroxy-5-oxo-4-[(1E)-phenylmethylene]amino}-4,5-dihydrothienof[3,2-b]pyridine-6-carboxamide

The products of Example 304D (1.55g, 5.57 mmol) and Example 268C (1.27 g, 3.71 mmol) in toluene (100 mL) were reacted at 118°C for 5 hours. The cooled slurry was filtered, washed with 25 mL toluene and dried to give the title compounds.

Example 324B

4-amino-6-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-7-hydroxythienof[3,2-b]pyridin-5(4H)-one

The product of Example 324A (1.95g, 3.7mmole) was reacted with 10% aqueous potassium hydroxide (100 mL) at reflux for 24 hours, cooled to 25°C and acidified with concentrated hydrochloric acid to pH 2. The resulting solid was collected by filtration, washed repeatedly with water and dried to provide the title compound (2.05 g, 100%). MS (ESI-) m/z 467 (M-H)⁻.

Example 324C

6-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-(cyclohexylideneamino)-7-hydroxythienof[3,2-b]pyridin-5(4H)-one

The product of Example 324B (0.20 g, 0.42 mmol) and cyclohexanone (2.0g, 20 mmol) in N,N-dimethylacetamide (4 mL) were reacted at 130°C for 60 minutes in a microwave reactor in a sealed tube. The solvent was removed under reduced pressure and the resulting residue was triturated with diethyl ether (8 mL), filtered and dried to give the title compound (0.167g 73%).

Example 324D

6-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-(cyclohexylamino)-7-hydroxythieno[3,2-b]pyridin-5(4H)-one

The product of Example 324C (0.167g, .30 mmol) in tetrahydrofuran (6 mL) and methanol (0.030 mL, 0.8 mmol) at 0°C was reacted with lithium borohydride (2.0 M solution in tetrahydrofuran, 0.250 mL, 0.50 mmol). The reaction was stirred at 25°C for 1.5 hour, acidified to pH 2 with 1 M aqueous hydrochloric acid and diluted with water (25 mL). The resulting precipitate was collected by filtration and dried to constant weight to give the title compound (0.114 g, 69%). MS (APCI+) m/z 551 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.36 (m, 10 H) 5.25 (s, 2 H) 6.50 (s, 1 H) 7.43 (m, 8 H) 7.69 (d, J=8.82 Hz, 1 H) 8.29 (d, J=5.15 Hz, 1 H) 14.10 (s, 1 H) 14.87 (s, 1 H).

Example 324E

4-(cyclohexylamino)-7-hydroxy-6-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)thieno[3,2-b]pyridin-5(4H)-one

The product of Example 324D (0.114g, 0.21 mmol) in dry acetonitrile (11 mL) at 25°C was reacted with iodotrimethylsilane (0.29 mL, 2.1 mmol) at 50°C for 4 hours. The reaction was cooled to 25°C and diluted with water (50 mL). The resulting precipitate was collected by filtration and dried under reduced pressure to give the title compound (0.083g, 87% yield). MS (ESI-) m/z 459 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.20 (m, 5 H) 1.66 (m, 5 H) 6.51 (s, 1 H) 7.18 (m, 2 H) 7.48 (d, J=5.52 Hz, 1 H) 7.57 (d, J=9.56 Hz, 1 H) 8.29 (d, J=5.15 Hz, 1 H) 10.42 (s, 1 H) 14.04 (s, 1 H) 14.93 (s, 1 H).

Example 324F

2-({3-[4-(cyclohexylamino)-7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-b]pyridin-6-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 324E (0.209 g, 0.45mmol) was reacted with cesium carbonate (0.589 g, 1.81 mmol), 2-bromoacetamide (0.125 g, 0.91 mmol) and a catalytic amount of tetrabutylammonium iodide in N,N-dimethylformamide (8 mL) at 25°C for 18 hours. The reaction was diluted with 50 mL water, acidified to pH 2 with 1 M hydrochloric acid. The resulting precipitate was collected by filtration and purified by column

chromatography on silica gel eluting with 5% methanol in chloroform to give the title compound (0.050 g, 21% yield). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI-) m/z 516 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 1.48 (m, 10 H) 4.59 (s, 2 H) 6.50 (s, 1 H) 7.39 (m, 2 H) 7.44 (s, 1 H) 7.48 (d, $J=5.15$ Hz, 1 H) 7.65 (s, 1 H) 7.70 (d, $J=9.56$ Hz, 1 H) 8.28 (d, $J=5.15$ Hz, 1 H) 14.13 (s, 1 H) 14.89 (s, 1 H).

Example 325

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-(2-hydroxyethyl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added ethanolamine (2.8 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.7mg, 85.8%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 3.34 (m, 2 H), 3.51 (m, 2 H), 5.61 (m, 2 H), 7.29 (m, 5 H), 7.42 (m, 1 H), 7.52 (m, 1 H), 7.75 (m, 1 H), 7.96 (s, 1 H), 8.23 (m, 1 H), 8.37 (m, 1 H). MS (DCI⁺) m/z 525 (M+H)⁺.

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3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-2-hydroxy-1-(aminocarbonyl)ethyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added L-serinamide hydrochloride (6.5 mg, 1.1 equivalents) followed by N-methylmorpholine (12.6 μ L, 2.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (17.1mg, 73%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 3.69 (dd, $J=4.96, 3.13$ Hz, 2 H), 4.40 (m, 1 H), 5.62 (s, 2 H), 7.27 (m, 5 H), 7.41 (m, 1 H), 7.53 (m, 1 H), 7.75 (m, 1 H), 8.12 (s, 1 H), 8.22 (d, $J=7.72$ Hz, 1 H), 8.28 (d, $J=7.72$ Hz, 1 H). MS (DCI⁺) m/z 568 (M+H)⁺.

Example 327N-(2-amino-2-oxoethyl)-3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added glycine hydrochloride (5.1 mg, 1.1 equivalents) followed by N-methylmorpholine (14 μ L, 3 equivalents) and the solution was stirred for 3 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (17 mg, 76%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 3.83 (d, $J=5.52$ Hz, 2 H), 5.61 (s, 2 H), 7.13 (s, 1 H), 7.32 (m, 6 H), 7.51 (d, $J=8.09$ Hz, 1 H), 7.75 (m, 1 H), 8.04 (s, 1 H), 8.21 (d, $J=6.99$ Hz, 1 H), 8.59 (t, $J=5.88$ Hz, 1 H). MS (DCI^+) m/z 538 ($\text{M}+\text{H}$) $^+$.

Example 3283-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-2-hydroxy-1-methylethyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added (S)-(+)-2-amino-1-propanol (3.6 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.4 mg, 82%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 3.46 (m, 2 H), 3.95 (m, 1 H), 5.62 (s, 2 H), 7.30 (m, 5 H), 7.41 (t, $J=7.72$ Hz, 1 H), 7.52 (d, $J=8.82$ Hz, 1 H), 7.74 (d, $J=6.99$ Hz, 1 H), 7.96 (s, 1 H), 8.10 (d, $J=8.09$ Hz, 1 H), 8.22 (d, $J=6.99$ Hz, 1 H). MS (DCI^+) m/z 539 ($\text{M}+\text{H}$) $^+$.

Example 3293-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N,N-bis(2-hydroxyethyl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added diethanolamine

(4.43 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (6.85 mg, 29%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 3.53 (m, 4 H), 5.62 (s, 2 H), 7.30 (m, 6 H), 7.41 (t, $J=7.54$ Hz, 1 H), 7.53 (d, $J=8.46$ Hz, 1 H), 7.59 (s, 1 H), 7.76 (m, 1 H), 8.22 (d, $J=8.09$ Hz, 1 H). MS (ESI $^+$) m/z 569 (M+H) $^+$.

Example 330

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-hydroxy-1-(hydroxymethyl)ethyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added serinol (4.21 mg, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.2 mg, 79%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 3.51 (d, $J=5.52$ Hz, 4 H), 3.89 (m, $J=6.25$ Hz, 1 H), 5.63 (s, 2 H), 7.30 (m, 6 H), 7.42 (t, $J=7.54$ Hz, 1 H), 7.53 (d, $J=8.82$ Hz, 1 H), 7.75 (d, $J=8.46$ Hz, 1 H), 8.02 (m, 2 H), 8.22 (d, $J=8.09$ Hz, 1 H). MS (DCI $^+$) m/z 555 (M+H) $^+$.

Example 331

1-benzyl-4-hydroxy-3-(7-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl)quinolin-2(1H)-one

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added (R)-(+)-3-pyrrolidinol (3.84 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (19.8 mg, 87%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 1.89 (m, 2 H), 3.55 (m, 2 H), 4.31 (d, 1 H), 4.99 (br. s., 1 H), 5.62 (s, 2 H), 7.31 (m, 6 H), 7.41 (t, $J=7.54$ Hz, 1 H), 7.53 (d, $J=8.82$ Hz, 1 H), 7.69

(d, $J=6.99$ Hz, 1 H), 7.76 (t, $J=7.35$ Hz, 1 H), 8.22 (d, $J=6.99$ Hz, 1 H). MS (ESI⁺) m/z 551 (M+H)⁺.

Example 332

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-(3-hydroxypropyl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added 2-(methylamino)-ethanol (2.8 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (19.2mg, 86%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 1.67 (m, 2 H), 3.28 (m, 2 H), 3.48 (t, $J=6.25$ Hz, 2 H), 5.61 (s, 2 H), 7.30 (m, 6 H), 7.41 (t, $J=7.54$ Hz, 1 H), 7.52 (d, $J=8.46$ Hz, 1 H), 7.75 (t, $J=6.99$ Hz, 1 H), 7.92 (s, 1 H), 8.21 (m, 1 H), 8.34 (t, $J=5.33$ Hz, 1 H). MS (DCI⁺) m/z 539 (M+H)⁺.

Example 333

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(2S)-2,3-dihydroxypropyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added (S)-(-)-3-amino-1,2-propanediol (4.21 mg, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.4mg, 80%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 3.15 (m, 2 H), 3.60 (m, 2 H), 5.62 (s, 2 H), 7.30 (m, 6 H), 7.41 (t, $J=7.54$ Hz, 1 H), 7.52 (d, $J=8.46$ Hz, 1 H), 7.75 (m, 1 H), 7.98 (s, 1 H), 8.22 (d, $J=6.62$ Hz, 1 H), 8.32 (t, $J=5.88$ Hz, 1 H). MS (DCI⁺) m/z 555 (M+H)⁺.

Example 334

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-1-(hydroxymethyl)propyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and

1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added (S)-(+)-2-amino-1-butanol (4.36 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (16.5 mg, 72%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 0.91 (t, $J=7.35$ Hz, 3 H), 1.54 (m, 2 H), 3.45 (m, 2 H), 3.81 (m, 1 H), 5.62 (s, 2 H) 7.31 (m, 6 H), 7.41 (t, $J=7.72$ Hz, 1 H), 7.52 (d, $J=8.09$ Hz, 1 H), 7.76 (t, $J=7.91$ Hz, 1 H), 7.98 (m, 1 H), 8.01 (d, $J=8.46$ Hz, 1 H), 8.22 (d, $J=6.99$ Hz, 1 H). MS (DCI $^+$) m/z 553 (M+H) $^+$.

Example 335

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-1-(hydroxymethyl)-2-methylpropyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added (S)-(+)-2-amino-3-methyl-1-butanol (5.15 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.8 mg, 80%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 0.92 (dd, $J=6.62$, 5.15 Hz, 6 H), 1.95 (m, 1 H), 3.48 (d, $J=5.88$ Hz, 2 H), 3.80 (m, 1 H), 5.62 (s, 2 H), 7.30 (m, 6 H), 7.40 (t, $J=7.72$ Hz, 1 H), 7.51 (d, $J=8.46$ Hz, 1 H), 7.75 (m, 1 H), 7.95 (d, $J=8.82$ Hz, 1 H), 8.00 (s, 1 H), 8.22 (d, $J=6.62$ Hz, 1 H). MS (DCI $^+$) m/z 567 (M+H) $^+$.

Example 336

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-hydroxybutyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added 1-amino-2-butanol (4.43 μ L, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water,

methanol and diethyl ether to give the title compound as a white solid (19.97 mg, 87%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (t, J=7.35 Hz, 3 H), 1.41 (m, 2 H), 3.14 (m, 2 H), 3.50 (m, 1 H), 5.62 (s, 2 H), 7.29 (m, 6 H), 7.41 (t, J=7.72 Hz, 1 H), 7.52 (d, J=8.82 Hz, 1 H), 7.74 (m, J=8.09 Hz, 1 H), 7.97 (s, 1 H), 8.21 (m, 1 H), 8.31 (t, J=5.33 Hz, 1 H). MS (DCI⁺) m/z 553 (M+H)⁺.

Example 337

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-hydroxy-2-(4-hydroxyphenyl)ethyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added octopamine hydrochloride (8.6 mg, 1.1 equivalents) followed by N-methylmorpholine (12.6 μL, 2.72 equivalents) and the solution was stirred for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (13.58 mg, 53%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 4.63 (dd, J=7.72, 4.41 Hz, 1 H), 5.62 (s, 2 H), 6.72 (d, J=8.46 Hz, 2 H), 7.18 (d, J=8.46 Hz, 2 H), 7.31 (m, 6 H), 7.41 (t, J=7.54 Hz, 1 H), 7.52 (d, J=8.82 Hz, 1 H), 7.74 (t, J=6.99 Hz, 1 H), 7.94 (s, 1 H), 8.21 (m, 1 H), 8.42 (t, J=5.52 Hz, 1 H), 9.27 (s, 1 H). MS (ESI) m/z 615 (M-H)⁻.

Example 338

1-benzyl-3-[1,1-dioxido-7-(piperazin-1-ylcarbonyl)-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added piperazine (4 mg, 1.1 equivalents) followed by N-methylmorpholine (8 μL, 1.72 equivalents) and the solution was stirred for 16 hours. Water (5 mL) was added and the resulting precipitate was collected by filtration and washed with water, methanol and diethyl ether to give the title compound as a white solid (18.3 mg, 80.16%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 3.14 (s, 4 H), 3.65 (m, 4 H), 5.43 (s, 2 H), 7.26 (m, 8 H), 7.46 (m, 2 H), 8.11 (t, J=7.72 Hz, 1 H), 8.70 (br.s, 1 H). MS (DCI⁺) m/z 550 (M+H)⁺.

Example 339N-[5-(aminocarbonyl)pyridin-2-yl]-3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide

A solution of the product of Example 318 (20 mg, 0.042 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.76 mg, 1.48 equivalents), and 1-hydroxybenzotriazole (8.66 mg, 1.54 equivalents) in N,N-dimethylformamide (0.4 mL) was stirred for 15 minutes at room temperature. To this mixture was added 6-aminonicotinamide (6.33 mg, 1.1 equivalents) followed by N-methylmorpholine (8 μ L, 1.72 equivalents) and the solution was heated at 70 °C for 16 hours. A solution of 1 N hydrochloric acid (4 mL) was added and the resulting precipitate was collected by filtration and washed with water, and diethyl ether. The solid was dissolved in 5% methanol/dichloromethane with 2 drops of triethylamine and purified by flash chromatography on silica gel using a Biotage-12s column eluting with 10:90 methanol/dichloromethane to give the title compound as a white solid (5.4 mg, 21.6%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ^1H NMR (300 MHz, DMSO- d_6) δ 5.64 (s, 2 H), 7.30 (m, 6 H), 7.43 (t, $J=7.54$ Hz, 1 H), 7.50 (m, 1 H), 7.54 (d, $J=8.46$ Hz, 1 H), 7.76 (m, 1 H), 8.10 (s, 1 H), 8.24 (m, 2 H), 8.32 (m, 1 H), 8.38 (s, 1 H), 8.88 (d, $J=1.84$ Hz, 1 H), 11.17 (s, 1 H). MS (DCI $^+$) m/z 601 (M+H) $^+$.

Example 340Aethyl 2-(isopentylamino)nicotinate

A mixture of ethyl 2-chloronicotinate (3.71 g, 20 mmol), isoamylamine (3.03 mL, 26 mmol) and triethylamine (3.62 mL, 26 mmol) was heated in a sealed tube at 140°C for 8 hours, cooled to 25°C, diluted with ethyl acetate and the mixture washed with water. The organic layer was extracted with 1N aqueous hydrochloric acid. The acidic aqueous layer was adjusted to pH 8.0 with saturated sodium bicarbonate solution then extracted with ethyl acetate (2 portions). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound (3.58 g, 76%). MS (DCI/NH $_3$) m/z 237 (M+H) $^+$. ^1H NMR (300 MHz, DMSO- d_6) δ ppm 0.93 (d, $J=6.25$ Hz, 6 H) 1.31 (t, $J=6.99$ Hz, 3 H) 1.47 (q, $J=6.99$ Hz, 2 H) 1.64 (m, 1 H) 3.47 (m, 2 H) 4.28 (q, $J=6.99$ Hz, 2 H) 6.59 (dd, $J=7.72$, 4.78 Hz, 1 H) 7.90 (t, $J=5.15$ Hz, 1 H) 8.07 (dd, $J=7.91$, 2.02 Hz, 1 H) 8.28 (dd, $J=4.78$, 1.84 Hz, 1 H).

Example 340B2-(isopentylamino)nicotinic acid

A mixture of Example 340A (1.73 g, 7.31 mmol), 1N aqueous sodium hydroxide (14.6 mL), and methanol (7 mL) was stirred for 18 hours and diluted with water. The

aqueous mixture was washed with ethyl acetate followed by dichloromethane, and adjusted to pH 7.5 with 1N aqueous hydrochloric acid. The resulting precipitate was collected by vacuum filtration, washed with water and air dried to give the title compound (424.4 mg, 28%). MS (DCI/NH₃) m/z 209 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ ppm 0.91 (d, J=6.62 Hz, 6 H) 1.46 (q, J=6.99 Hz, 2 H) 1.63 (m, 1 H) 3.45 (t, J=7.17 Hz, 2 H) 6.56 (dd, J=7.72, 4.78 Hz, 1 H) 8.04 (dd, J=7.72, 1.84 Hz, 1 H) 8.05 (m, 1 H) 8.25 (dd, J=4.78, 2.21 Hz, 1 H) 12.96 (s, 1 H).

Example 340C

4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of Example 340B (1 g, 4.81 mmol), acetic anhydride (10 mL) and glacial acetic acid (10 mL) was heated at 130°C for 2 hours. The mixture was cooled to 25°C and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 0-100% hexane in ethyl acetate step gradient to give the title compound (100 mg, 9%). MS (DCI/NH₃) m/z 233 (M+H)⁺. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 0.94 (d, J=6.62 Hz, 6 H) 1.46 (m, 2 H) 1.60 (m, 1 H) 4.33 (m, 2 H) 5.88 (s, 1 H) 7.27 (dd, J=7.72, 4.78 Hz, 1 H) 8.22 (dd, J=7.72, 1.84 Hz, 1 H) 8.65 (dd, J=4.78, 1.84 Hz, 1 H) 11.61 (s, 1 H).

Example 340D

3-[bis(methylthio)methylene]-1-butyl-1,8-naphthyridine-2,4(1H,3H)-dione

A solution of the product of Example 340C (0.2 g, 0.86 mmol) in dimethylformamide (7 mL) was treated with sodium hydride (76 mg, 60% in mineral oil, 2.2 equivalents), stirred for 30 min at 25°C, treated with carbon disulfide (0.14 g, 2.2 eq.), heated at 50°C for 6 hours, cooled to 25°C, and treated with methyl iodide (0.27 g, 2.2 eq.). The mixture was stirred at 25°C for 18 hours and concentrated. The residue was triturated with water and the resulting solids were filtered and dried in vacuo to give the title compound (0.23 g, crude yield 80%). ¹H NMR (300 MHz, DMSO-d₆) δ 1.00 (d, J=10 Hz, 6 H), 1.6 (m, 2H), 1.75 (m, 1H), 2.63 (s, 6H), 4.4 (m, 2H), 7.1 (dd, J=10 Hz, 7 Hz, 1H), 8.42 (dd, J=10 Hz, 3 Hz, 1H), 8.58 (dd, J=7 Hz, 3 Hz, 1H). MS (DCI+) m/z 337 (M+H)⁺.

Example 340E

4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl}-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 309G (37.5 mg, 0.15 mmol) and the product of Example 340D (50 mg, 0.15 mmol) were reacted in toluene (5 mL) at 100°C for 3 hours. The reaction was concentrated under reduced pressure and the residue was purified by chromatography on

silica gel using a Biotage-12m column eluting with 2:98 methanol:dichloromethane to give the title compound as a yellow solid (36mg, 49%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, *J*=6.99 Hz, 6 H), 1.57 (m, 2 H), 1.66 (m, 1 H), 4.45 (d, *J*=7.35 Hz, 2 H), 4.64 (s, 3 H), 4.71 (s, 3 H), 7.43 (s, 1 H), 7.46 (m, 1 H), 8.54 (d, *J*=6.99 Hz, 1 H), 8.87 (s, 1 H), 14.45 (br.s, 1 H). MS (DCI⁺) *m/z* 510 (M+NH₄)⁺.

Example 341

4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one

The product of Example 340C (23 mg, 0.05 mmol) was reacted with 6 N aqueous hydrochloric acid (1 mL) in tetrahydrofuran (2 mL) at 70°C for 3 hours. The reaction was concentrated under reduced pressure to remove the tetrahydrofuran, and treated with methanol (5 mL). The resulting precipitate was collected by filtration and washed with water and diethyl ether to give the title compound as a white solid (13 mg, 62%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, *J*=6.62 Hz, 6 H), 1.57 (m, 2 H), 1.67 (m, 1 H), 4.46 (m, 2 H), 4.62 (s, 2 H), 7.30 (s, 1 H), 7.47 (dd, *J*=8.09, 4.78 Hz, 1 H), 8.54 (dd, *J*=7.72, 1.84 Hz, 1 H), 8.86 (m, 1 H), 14.39 (br.s, 1 H). MS (DCI⁺) *m/z* 466 (M+NH₄)⁺.

Example 342

[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl]methyl carbamate

A suspension of the product of Example 310 (40 mg, 0.086 mmol) in a solution of N,N-dimethylformamide (2 mL) and acetonitrile (0.6 mL) at -20°C was treated with chlorosulfonyl-isocyanate (16.4 μL, 2.2 equivalents). The mixture was stirred 0.5 hour at -20°C and 2 hours at 0°C, 6N hydrochloric acid (2 mL) was added and the mixture was heated 2.5 hours at 70°C. The mixture was cooled and water (10 mL) was added, the resulting precipitate was collected by filtration and washed with water and diethyl ether. The solid was dissolved in 5% methanol/dichloromethane with a few drops of triethylamine and purified by flash chromatography on silica gel using a Biotage-12s column eluting with 6:94 methanol/ dichloromethane to give the title compound as a white solid (23 mg, 52.6%). The sodium salt of the title compounds was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 5.08 (s, 2 H), 5.62 (s, 2 H), 6.72 (s, 2 H), 7.29 (m, 5 H), 7.42 (m, 2 H), 7.53 (d, *J*=8.82 Hz, 1 H), 7.77 (t, *J*=7.35 Hz, 1 H), 8.22 (d, *J*=6.99 Hz, 1 H). MS (DCI⁺) *m/z* 528 (M+NH₄)⁺.

Example 343

[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl aminocarbonylcarbamate

A suspension of the product of Example 310 (40 mg, 0.086 mmol) in a solution of
5 N,N-dimethylformamide (2 mL) and acetonitrile (0.6 mL) at -20°C was treated with
chlorosulfonyl-isocyanate (16.4 µL, 2.2 equivalents). The mixture was stirred 0.5 hour at -
20°C and 2 hours at 0°C, 6N hydrochloric acid (2 mL) was added and the mixture was heated
2.5 hours at 70 °C. The mixture was cooled and water (10 mL) was added, the resulting
precipitate was collected by filtration and washed with water and diethyl ether. The solid
10 was dissolved in 5% methanol/dichloromethane with a few drops of triethylamine and
purified by flash chromatography on silica gel using a Biotage-12s column eluting with 6:94
methanol/ dichloromethane to give the title compound (6 mg, 12.7%). The sodium salt of the
title compound was prepared according to the procedure of Example 1D. ¹H NMR (300
MHz, DMSO-d₆) δ 5.23 (s, 2 H), 5.61 (s, 2 H), 7.28 (m, 4 H), 7.35 (m, 2 H), 7.51 (m, 1 H),
15 8.20 (m, 2 H), 10.01 (s, 1 H). MS (ESI⁺) m/z 552 (M-H)⁺.

Example 344

3-[7-(azidomethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-1-benzyl-4-hydroxyquinolin-2(1H)-one

To the solution of the product of Example 310 (156.4 mg, 0.33 mmol) in
20 dichloromethane (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.37 mL, 2.47
mmol) and diphenylphosphoryl azide (0.54 mL, 2.50 mmol) at room temperature. The
solution was stirred at room temperature overnight and concentrated *in vacuo*. The residue
was diluted with ethanol and aqueous hydrogen chloride (1 N, 2 mL) was added slowly and
precipitates appeared. The solid was filtered and rinsed with a solution of ethanol/water (2:1)
25 to give the title compound as a light brown solid (124.47 mg, 76%). MS (ESI⁺) m/z 491 (M-
H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 4.59 (s, 2 H) 5.62 (br s, 2 H) 7.30 (m, 5 H) 7.41 (t,
J=7.54 Hz, 1 H) 7.52 (d, *J*=8.82 Hz, 1 H) 7.58 (s, 1 H) 7.76 (m, 1 H) 8.22 (dd, *J*=8.09, 1.47
Hz, 1 H).

Example 345

30 3-[7-(aminomethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-1-benzyl-4-hydroxyquinolin-2(1H)-one

To the solution of the product of Example 344 (136.2 mg, 0.28 mmol) in pyridine
(1.68 mL) and concentrated ammonium hydroxide (1.12 mL) was added triphenylphosphine
(145 mg, 0.55 mmol) at room temperature. The solution was stirred at room temperature
35 overnight and concentrated *in vacuo*. The residue was diluted with toluene and the solid was
filtered to give the title compound as a light brown solid (100.78 mg, 78%). MS (ESI⁺) m/z
467 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 4.10 (s, 2 H) 5.41 (br s, 2 H) 7.07-7.32 (m,

8 H) 7.43 (m, 1 H) 8.10 (dd, $J=7.91$, 1.65 Hz, 1 H).

Example 346

N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}methanesulfonamide

5 To a solution of the product of Example 345 (15mg, 0.032 mmol) in tetrahydrofuran (0.4 mL) was added triethylamine (0.018 mL, 0.129 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.018 mL, 0.129 mmol). The mixture was cooled to 0°C and methanesulfonyl chloride was added (0.003 mL, 0.032 mmol). The mixture was stirred at 0°C for 2.5 hours and then warmed to 23°C and stirred for 2.5 hours. Additional 1,8-
10 diazabicyclo[5.4.0]undec-7-ene (0.010 mL, 0.064 mmol) and methane sulfonyl chloride (0.003 mL, 0.032 mmol) were added and the mixture was stirred at 23°C for 15 hours. A few drops of N,N-dimethylformamide were added to increase solubility. Additional methane sulfonyl chloride (0.003 mL, 0.032 mmol) was added and the reaction mixture was stirred at 23°C for 3 hours. A few drops of N,N-dimethylformamide and methane sulfonyl chloride
15 (0.003 mL, 0.032 mmol) were added and the reaction mixture was stirred at 23°C for 1 hour. Additional methane sulfonyl chloride (0.006 mL, 0.064 mmol) was added and the reaction mixture was stirred at 23°C for 72 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was diluted with diethyl ether and 1 N hydrochloric acid was added until no further precipitation was observed. The precipitate was then washed with
20 water followed by diethyl ether. The solid was dissolved in 1% triethylamine/dichloromethane and purified by preparative thin layer chromatography eluting with 5% (5% triethylamine/ methanol)/ dichloromethane. The silica gel was washed with 10% (5% triethylamine/ methanol)/ dichloromethane to give the triethylamine salt of the title compound (4.7 mg, 23%). ¹H NMR (500 MHz, DMSO-d₆) δ 1.16 (t, $J=6.71$ Hz, 9 H) 2.94
25 (s, 3 H) 3.08 (bs, 6 H) 4.26 (d, 2 H) 5.40 (bs, 2 H) 7.06 (m, 2 H) 7.12 (d, $J=8.54$ Hz, 1 H) 7.23 (m, 5 H) 7.40 (t, $J=7.32$ Hz, 1 H) 7.50 (t, $J=6.41$ Hz, 1 H) 8.10 (d, $J=6.10$ Hz, 1 H).

Example 347

N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}nicotinamide

30 To the solution of the product of Example 345 (0.015 g, 0.032 mmol) in tetrahydrofuran (0.4 mL) was added triethylamine (0.022 mL, 0.160 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.020 mL, 0.129 mmol). The mixture was cooled to 0°C and nicotinoylchloride hydrochloride (0.007 g, 0.035 mmol) was added. The mixture was stirred for 2.5 hours and then warmed to 23°C and stirred for 2.5 hours. Additional 1,8-
35 diazabicyclo[5.4.0]undec-7-ene (0.010 mL, 0.068 mmol) and nicotinoylchloride hydrochloride (0.006 g, 0.032 mmol) were added and the mixture was stirred at 23°C for 15 hours. Added additional nicotinoyl chloride hydrochloride (0.006g, 0.032 mmol) and stirred

at 23⁰C for 6 hours. A few drops of N,N-dimethylformamide were added to increase solubility. Added additional nicotinoyl chloride hydrochloride (0.006g, 0.032 mmol) and stirred at 23⁰C for 72 hours. Hydrochloric acid (4 M in dioxane) (0.095 mL, 0.370 mmol) was added and the reaction mixture was concentrated under reduced pressure. The resulting solid was then washed with diethyl ether and water. The solid was dissolved in 1% triethylamine/ dichloromethane and purified by preparative thin layer chromatography eluting with 5%(5% triethylamine/ methanol)/ dichloromethane. The silica gel was washed with 10% (5% triethylamine/ methanol)/ dichloromethane to give the triethylamine salt of the title compound (0.0068 g, 31%). ¹H NMR (500 MHz, DMSO-d₆) δ 1.17 (t, J=7.32 Hz, 9 H) 3.09 (q, J=7.32 Hz, 6 H) 4.60 (d, J=4.88 Hz, 2 H) 5.44 (bs, 2 H) 7.00 (bs, 1 H) 7.12 (m, 1 H) 7.26 (m, 5 H) 7.46 (m, 1 H) 7.53 (dd, J=7.63, 4.58 Hz, 1 H) 8.12 (d, J=7.32 Hz, 1 H) 8.26 (m, J=7.93 Hz, 1 H) 8.72 (d, J=3.66 Hz, 1 H) 8.86 (bs, 1 H) 9.09 (s, 1 H) 9.16 (bs, 1 H).

Example 348

N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}morpholine-4-carboxamide

To the solution of the product of Example 345 (0.015 g, 0.032 mmol) in tetrahydrofuran (0.4 mL) was added triethylamine (0.009 mL, 0.064 mmol). The mixture was cooled to 0⁰C and 4-morpholinecarbonyl chloride (0.004 mL, 0.035 mmol) was added. The reaction mixture was warmed to 23⁰C and stirred for 15 hours. 1 N hydrochloric acid (0.065 mL, 0.064 mmol) was added and the mixture was then concentrated under reduced pressure. The product was washed with diethyl ether and water to give the title compound (7.5 mg, 40%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (500 MHz, DMSO-d₆) δ 3.57 (t, 4 H) 4.38 (d, J=4.88 Hz, 2 H) 5.60 (bs, 2 H) 7.11 (m, 2 H) 7.27 (m, 6 H) 7.38 (m, J=7.32, 3.05 Hz, 1 H) 7.49 (m, J=7.32 Hz, 1 H) 7.73 (bs, 1 H) 8.21 (d, J=7.32 Hz, 1 H).

Example 349

N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}-2-hydroxyacetamide

To the solution of the product of Example 345 (0.0226 g, 0.048 mmol) in N,N-dimethylformamide (0.5 mL) was added triethylamine (0.020 mL, 0.145 mmol), 4-(dimethylamino)pyridine (0.018 g, 0.145 mmol), glycolic acid (0.011 g, 0.145 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.028 g, 0.145 mmol). The mixture was stirred at 23⁰C for 15 hours and then was heated to 60⁰C and stirred for 20 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was diluted with dichloromethane, cooled to 0⁰C, and hydrochloric acid (4 M in dioxane) was added (0.037 mL, 0.145 mmol). The mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10%

acetonitrile in 0.1% trifluoroacetic acid/ water to 95% acetonitrile in 0.1%trifluoroacetic acid/
water to give the title compound (10.8 mg, 42%). The sodium salt of the title compound was
prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 3.91
(s, 2 H) 4.44 (d, J=5.88 Hz, 2 H) 5.61 (bs, 2 H) 7.14 (s, 1 H) 7.29 (m, 5 H) 7.41 (t, J=7.35
5 Hz, 1 H) 7.52 (d, J=9.19 Hz, 1 H) 7.75 (t, 1 H) 8.21 (dd, 1 H) 8.35 (t, 1 H).

Example 350A

1-amino-4-hydroxyquinolin-2(1H)-one

To a solution of 25% by weight aqueous potassium hydroxide (200 mL) and 1,4-
10 dioxane (50 mL) heated to 90-100°C was added portion wise the product of Example 226C
(6.72 g, 20.0 mmol). The reaction mixture was heated at reflux for 90 minutes allowing
distillation to occur and additional water and dioxane (30 mL each) were added to the
reaction vessel to reach the original volume. The mixture was refluxed for an additional 90
minutes with distillation, cooled, washed with 200 mL of 1:1 diethyl ether/ethyl acetate,
15 acidified with concentrated hydrochloric acid to pH 2 and the resulting solid was collected by
filtration, washed with water and dried to constant mass to give the title compound as a tan
solid (3.22 g, 91% yield). MS (DCI) m/z 177 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ
5.56 (s, 2 H) 5.94 (s, 1 H) 7.20 (t, J=7.54 Hz, 1 H) 7.62 (m, 1 H) 7.85 (m, 2 H) 11.33 (s, 1 H).

Example 350B

2-(4-hydroxy-2-oxoquinolin-1(2H)-yl)-1H-isoindole-1,3(2H)-dione

A mixture of the product of Example 350A (0.54 g, 3 mmol), phthalic anhydride
(1.36 g, 2.2 eq.) and diisopropylethylamine (1.97 g, 5 eq.) in dioxane (20 mL) was heated at
100°C for 2 hours, cooled to 25°C and concentrated. The residue was triturated with water
25 and ether. The resulting solids were filtered and dried in vacuum to give the title compound
(0.6 g, 64% crude yield) which was used directly for the next step. ¹H NMR (300 MHz,
DMSO-d₆) δ 5.95 (s, 1H), 7.37 (m, 1H), 7.6 (m, 2H), 7.95-8.1 (m, 5H), 12.18 (s, 1H). MS
(DCI⁺) m/z 306 (M+H)⁺.

Example 350C

3-[bis(methylthio)methylene]-1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)quinoline- 2,4(1H,3H)-dione

A solution of the product of Example 350B (0.6 g, 1.96 mmol) in acetic acid:pyridine
(5:1, 15 mL) was treated with tris(methylthio)methyl methyl sulfate (prepared using the
35 procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A.
Gatti, V. Regondi)(1.6 g, 3 eq.) and heated at 100°C for 2 hours. The reaction mixture was

treated with ice, and the precipitated solids were filtered and dried in vacuum to give 0.53 g (66 %) of the title compound. ¹H NMR (300 MHz, DMSO-d₆) δ 2.63 (s, 6H), 7.34 (m, 1H), 7.55 (d, 1H), 7.61 (m, 1H), 8.08 (m, 5H). MS (DCI+) m/z 411 (M+H)⁺.

Example 350D

5 2-[4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-
e][1,2,4]thiadiazin-3-yl}-2-oxoquinolin-1(2*H*)-yl]-1*H*-isoindole-1,3(2*H*)-dione

The product of Example 309G (32.6 mg, 0.13 mmol) and the product of Example 350C (53 mg, 0.13 mmol) were reacted in toluene (3 mL) at 100°C for 3 hours. The resulting precipitate was collected by filtration and washed with methanol and diethyl ether to give the title compound (45 mg, 61.5%). ¹H NMR (300 MHz, DMSO-d₆) δ 3.32 (s, 3 H), 4.61 (s, 2 H), 4.70 (s, 2 H), 7.28 (s, 1 H), 7.42 (m, 1 H), 7.70 (d, *J*=4.04 Hz, 2 H), 8.06 (m, 2 H), 8.11 (m, 2 H), 8.22 (d, *J*=8.09 Hz, 1 H). MS (ESI) m/z 565 (M-H)⁻.

Example 350E

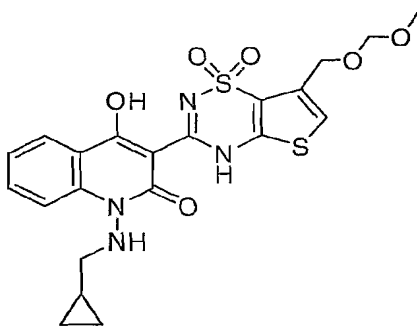
15 1-amino-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-
e][1,2,4]thiadiazin-3-yl}quinolin-2(1*H*)-one

A solution of the product of Example 350D (185 mg, 0.326 mmol), methylhydrazine (43.47 μL, 2.5 equivalents), and triethylamine (0.126 mL, 3 equivalents) in 1,4-dioxane (10 mL) was heated at 102°C for 3 hours. The reaction was concentrated under reduced pressure, and treated with a solution of methanol (75 mL) and 1N hydrochloric acid (100 mL). The resulting precipitate was collected by filtration and washed with water and diethyl ether to give the title compound as a white solid (94 mg, 66%). ¹H NMR (300 MHz, DMSO-d₆) δ 4.65 (s, 2 H), 4.71 (s, 2 H), 5.84 (br.s, 1 H), 7.44 (m, 2 H), 7.88 (m, 1 H), 8.04 (d, 1 H), 8.15 (d, 1 H), 14.73 (br.s, 2 H). MS (ESI) m/z 435 (M-H)⁻.

Example 350F

25 1-{[cyclopropylmethylene]amino}-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-
4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl}quinolin-2(1*H*)-one

The product of Example 350D (94 mg, 0.22 mmol) was reacted with cyclopropanecarbaldehyde (0.162 mL, 2.2 mmol) in N,N-dimethylacetamide (1 mL) in a sealed tube at 120°C for 90 minutes in a microwave reactor. The reaction was cooled to 25°C and concentrated under reduced pressure. The resulting residue was triturated with diethyl ether and filtered to give the title compound (78.9 mg, 75%).

Example 350G

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-[(methoxymethoxy)methyl]-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]quinolin-2(1H)-one

The product of Example 350F (78.9 mg, 0.16 mmol) in tetrahydrofuran (4 mL) and methanol (0.013 mL, 0.32 mmol) at 0°C was treated dropwise with a 2.0 M solution of lithium borohydride in tetrahydrofuran (0.131 mL, 0.24 mmol). The reaction was stirred at 25°C for 1 hour, acidified with 1N hydrochloric acid to approximately pH 2-4, diluted with water (20 mL), and the resulting precipitate was collected by filtration and dried. The crude product was chromatographed on silica gel with 2% methanol/ dichloromethane to give the title compound (41.6 mg, 52.5%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.15 (d, J=4.41 Hz, 2 H), 0.42 (d, J=8.09 Hz, 2 H), 1.01 (m, 1 H), 2.84 (d, J=6.62 Hz, 2 H), 4.64 (s, 2 H), 4.71 (s, 2 H), 6.36 (br.s, 1 H), 7.41 (m, 2 H), 7.88 (t, J=7.35 Hz, 1 H), 8.07 (d, J=8.46 Hz, 1 H), 8.16 (d, J=8.09 Hz, 1 H). MS (ESI⁺) m/z 489 (M-H)⁺.

Example 351

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]quinolin-2(1H)-one

The product of Example 350G (35 mg, 0.07 mmol) at 0°C was treated with 4 N solution of hydrogen chloride in 1,4-dioxane (1 mL). The reaction was stirred at 0°C for 2 hour and 25°C for 3 hour, basified with 10% sodium bicarbonate (3 mL) and extracted with 2% methanol/ dichloromethane. The solvent was concentrated and the residue was purified by flash column chromatography on silica gel eluting with 7% methanol/dichloromethane to give the title compound as a white solid (20 mg, 62.7%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.15 (d, J=4.04 Hz, 2 H), 0.42 (d, J=8.09 Hz, 2 H), 1.01 (m, 1 H), 2.81 (d, 2 H), 4.62 (s, 2 H), 5.55 (br.s, 1 H), 6.35 (br.s, 1 H), 7.28 (s, 1 H), 7.39 (m, 1 H), 7.85 (m, 1 H), 8.03 (m, 1 H), 8.15 (d, J=7.35 Hz, 1 H). MS (ESI⁺) m/z 489 (M-H)⁺.

Example 352Aethyl 3-{[2-(aminosulfonyl)-4-(benzyloxy)phenyl]amino}-3-oxopropanoate

A suspension of the product of Example 304D (508.3 mg, 1.826 mmol) and triethylamine (0.47 mL, 3.394 mmol) in anhydrous dichloromethane (10 mL) was cooled to 0°C under a nitrogen atmosphere. Ethyl malonyl chloride (0.43 mL, 3.023 mmol) was added dropwise and the resulting gold colored solution was stirred at 0°C for 15 minutes, then at room temperature for 5 hours. The reaction was diluted with dichloromethane (50 mL) and washed with water (20 mL). The aqueous wash was extracted with dichloromethane (25 mL), and the combined organic layers were washed with 1N aqueous hydrochloric acid (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The yellow oil was purified by column chromatography on silica gel eluting with a gradient of 12% to 15% ethyl acetate/dichloromethane to give the title compound as a white solid (340 mg, 47%). MS (ESI) m/z 391 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.22 (t, $J=7.17$ Hz, 3 H) 3.56 (s, 2 H) 4.14 (q, $J=6.99$ Hz, 2 H) 5.15 (s, 2 H) 7.27 (dd, $J=9.01, 3.13$ Hz, 1 H) 7.42 (m, 8 H) 7.75 (d, $J=8.82$ Hz, 1 H) 9.42 (s, 1 H).

Example 352Bethyl [7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]acetate

The product of Example 352A (292 mg, 0.744 mmol) and sodium carbonate (394 mg, 3.722 mmol) in anhydrous ethanol (12 mL) was heated to reflux under a nitrogen atmosphere for 6.5 hours. The reaction was cooled to room temperature, filtered, and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 3% methanol/dichloromethane to give the title compound as a white solid (237 mg, 85%). MS (ESI) m/z 373 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.21 (t, $J=6.99$ Hz, 3 H) 3.67 (s, 2 H) 4.16 (q, $J=6.99$ Hz, 2 H) 5.20 (s, 2 H) 7.39 (m, 8 H) 12.21 (s, 1 H).

Example 352Cethyl (7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

The product of Example 352B (277 mg, 0.7398 mmol) in ethanol (20 mL) was hydrogenated at 1 atmosphere hydrogen pressure (balloon) with 10% palladium on carbon (28 mg, 10 weight %) for 1.25 hour. The reaction was filtered through a PTFE membrane filter (0.45 μm) and the catalyst thoroughly washed with ethanol (50 mL). The filtrate was concentrated under reduced pressure and the resulting oil triturated with dichloromethane/hexanes (1:1 v/v) to give the title compound as a crystalline white solid (194 mg, 92%). MS (ESI) m/z 283 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.21 (t, $J=7.17$ Hz, 3 H) 3.64 (s, 2 H) 4.15 (q, $J=7.23$ Hz, 2 H) 7.06 (d, $J=2.57$ Hz, 1 H) 7.11 (dd,

$J=8.83$, 2.57 Hz, 1 H) 7.20 (d, $J=8.83$ Hz, 1 H) 10.21 (s, 1 H) 12.11 (s, 1 H).

Example 352D

ethyl (7-hydroxy-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

5 A suspension of the product of Example 352C (100 mg, 0.352 mmol) in glacial acetic acid (3 mL) was treated at room temperature with a solution of concentrated nitric acid in glacial acetic acid (1.43 M, 0.305 mL, 0.436 mmol) and stirred at this temperature for 19 hours. Added additional 1.43 M nitric acid/acetic acid (0.020 mL, 0.029 mmol) and let stir for 1.5 hours. The reaction was diluted with water (30 mL) and extracted with ethyl acetate
10 (2 x 50mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 8% methanol/dichloromethane to give the title compound as a light yellow solid (47 mg, 41%). MS (ESI) m/z 328 (M-H). ^1H NMR (300 MHz, PYRIDINE- d_5) δ 0.98 (t, $J=7.17$ Hz, 3 H) 3.86 (s, 2 H) 4.01 (q, $J=7.23$ Hz,
15 2 H) 7.11 (d, $J=8.82$ Hz, 1 H) 7.22 (d, $J=8.82$ Hz, 1 H).

Example 352E

ethyl (8-amino-7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)acetate

The product of Example 352D (61 mg, 0.1852 mmol) in methanol (5 mL) was hydrogenated at 1 atmosphere hydrogen pressure (balloon) with 10% palladium on carbon (9
20 mg, 15 weight %) for 45 minutes. The reaction was filtered through a PTFE membrane filter (0.45 μm) and the catalyst thoroughly washed with warm methanol (50 mL). The filtrate was concentrated under reduced pressure to give the title compound as a beige solid (55 mg, 99%). MS (ESI) m/z 298 (M-H). ^1H NMR (300 MHz, DMSO- d_6) δ 1.21 (t, $J=7.17$ Hz, 3 H) 3.61 (s, 2 H) 4.15 (q, $J=6.99$ Hz, 2 H) 5.22 (s, 2 H) 6.40 (d, $J=8.46$ Hz, 1 H) 6.93 (d,
25 $J=8.46$ Hz, 1 H) 9.82 (s, 1 H) 11.86 (s, 1 H).

Example 352F

ethyl (8-methyl-1,1-dioxido-4H-[1,3]oxazolo[5,4-*h*][1,2,4]benzothiadiazin-3-yl)acetate

A solution of the product of Example 352E (56.3 mg, 0.188 mmol) in anhydrous N,N-dimethylformamide (2 mL) was treated with trimethylorthoacetate (0.098 mL, 0.752 mmol)
30 and p-toluenesulfonic acid monohydrate (1 mg) at room temperature for 3 hours under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with 4% methanol/dichloromethane to give the title compound as a white crystalline solid (48 mg, 79%). MS (ESI) m/z 322 (M-H). ^1H NMR (300 MHz, DMSO- d_6) δ 1.22 (t, $J=7.17$ Hz, 3 H) 2.69 (s, 3 H) 3.71 (s, 2 H)
35 4.17 (q, $J=7.11$ Hz, 2 H) 7.27 (d, $J=8.82$ Hz, 1 H) 8.02 (d, $J=8.82$ Hz, 1 H) 12.33 (s, 1 H).

Example 352G

4-hydroxy-1-(3-methylbutyl)-3-(8-methyl-1,1-dioxido-4H-[1,3]oxazolo[5,4-

h)[1,2,4]benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

To a solution of the product of Example 12A (16.7 mg, 0.0714 mmol) and the product of Example 352F (23.1 mg, 0.0714 mmol) in anhydrous tetrahydrofuran (2 mL) at 0°C was added sodium hydride (60%, 11.4 mg, 0.286 mmol) under a nitrogen atmosphere. The reaction was heated at reflux for 3 hours, cooled to 0°C, and treated with glacial acetic acid (0.165 mL). The resulting yellow solution was heated at reflux for 2 hours, cooled to 0°C, diluted with water (5 mL), and acidified with 1N aqueous hydrochloric acid to pH 3. The resulting precipitate was collected by filtration, washed with water and dried to give the title compound as a yellow solid (20 mg, 60%). MS (ESI) m/z 466 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J =6.25 Hz, 6 H) 1.58 (m, 2 H) 1.71 (m, 1 H) 2.73 (s, 3 H) 4.50 (m, 2 H) 7.50 (dd, J =7.72, 4.41 Hz, 1 H) 7.64 (d, J =8.82 Hz, 1 H) 8.10 (d, J =8.82 Hz, 1 H) 8.57 (dd, J =7.91, 2.02 Hz, 1 H) 8.89 (dd, J =4.60, 2.02 Hz, 1 H) 14.18 (s, 1 H). A suspension of the product of Example 352G (14.6 mg, 0.0312 mmol) in anhydrous tetrahydrofuran (3 mL) and distilled water (1 mL) was treated with 0.998 N aqueous sodium hydroxide (0.0313 mL, 0.0312 mmol) and the yellow solution mixed for 15 minutes. The solvent was removed under reduced pressure and the residue dried to afford the sodium salt of Example 352G (15 mg, 98%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J =6.25 Hz, 6 H) 1.48 (m, 2 H) 1.65 (m, 1 H) 2.67 (s, 3 H) 4.30 (m, J =8.82, 6.25 Hz, 2 H) 7.13 (dd, J =7.91, 4.60 Hz, 1 H) 7.21 (d, J =8.82 Hz, 1 H) 7.86 (d, J =8.82 Hz, 1 H) 8.38 (dd, J =8.09, 1.47 Hz, 1 H) 8.53 (m, J =2.94 Hz, 1 H) 16.09 (s, 1 H).

Example 353A1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

To the suspension of the product of Example 350A (1.033 g, 5.86 mmol) in methanol (58 mL) was added acetic acid (0.29 mL) and cyclopropylcarboxaldehyde (482 µL, 6.45 mmol) followed by the addition of sodium cyanoborohydride (744.6 mg, 11.85 mmol) at room temperature. The suspension was stirred at room temperature overnight and quenched with half saturated brine (100 mL) and sodium bicarbonate (425 mg, 5.06 mmol). The mixture was extracted with ethyl acetate (300 mL) and the organic layer was separated and washed with half saturated brine (2 x 50 mL). The combined aqueous layers were extracted with dichloromethane (2 x 100 mL). The combined organic solution was dried with magnesium sulfate, filtered and concentrated. The residue was used without any purification. ¹H NMR (300 MHz, DMSO-d₆) δ 0.09 (m, 2 H) 0.40 (m, 2 H) 0.95 (m, 1 H) 2.70 (t, J =6.43 Hz, 2 H) 5.91 (s, 1 H) 6.10 (t, J =6.07 Hz, 1 H) 7.21 (m, 1 H) 7.62 (t, J =7.17 Hz, 1 H) 7.87 (m, 2 H) 11.42 (br s, 1 H).

Example 353B3-[bis(methylthio)methylene]-1-[(cyclopropylmethyl)amino]quinoline-2,4(1H,3H)-dione

To the suspension of the product of Example 353A (984.4 mg, 4.28 mmol) in 1,4-dioxane (40 mL) was added pyridine (2.8 mL, 34.6 mmol) and tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi) (2.26 g, 8.55 mmol) at room temperature. The suspension was put in a preheated oil bath at 55°C and stirred for 15 minutes. To the solution was added another portion of tris(methylthio)methyl methyl sulfate (2.26 g, 8.55 mmol) and the mixture was stirred at 55°C for 15 minutes and cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was diluted with dichloromethane and loaded on a silica gel column and eluted with dichloromethane, 2% ethyl acetate/dichloromethane and then 5% ethyl acetate/dichloromethane to give the title compound (852.1 mg, 60%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.15 (m, 2 H) 0.42 (m, 2 H) 0.98 (m, 1 H) 2.61 (s, 6 H) 2.73 (t, *J*=6.43 Hz, 2 H) 6.05 (t, *J*=5.88 Hz, 1 H) 7.15 (m, 1 H) 7.64 (m, 1 H) 7.76 (d, *J*=8.09 Hz, 1 H) 7.98 (m, 1 H).

Example 353C1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-[(methoxymethoxy)methyl]-1,1-dioxido-4H-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]quinolin-2(1H)-one

A solution of the product of Example 353B (500.3, 1.5 mmol) and the product of Example 309G (377.62 mg, 1.5 mmol) in dioxane (15mL) was stirred at reflux for 1.5 hours and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with 0% to 10% ethyl acetate/dichloromethane to give the title compound (384.7 mg, 52%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.15 (m, 2 H) 0.42 (m, 2 H) 1.01 (m, 1 H) 2.84 (d, *J*=6.99 Hz, 2 H) 4.64 (s, 2 H) 4.71 (s, 2 H) 6.36 (br s, 1 H) 7.42 (m, 2 H) 7.86 (m, 1 H) 8.07 (d, *J*=8.46 Hz, 1 H) 8.16 (m, 1 H).

Example 353D3-[7-(azidomethyl)-1,1-dioxido-4H-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

To the product of Example 353C (384.7 mg, 0.78 mmol) was added a solution of hydrogen chloride in dioxane (4N, 7.8 mL) at 0°C. The solution warmed to room temperature and stirred for 5.5 hours and concentrated under reduced pressure. This solid was suspended in dichloromethane (7.8 mL) and to the suspension was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.6 mL, 4.01 mmol) and diphenylphosphoryl azide (0.85 mL, 3.94 mmol) at room temperature and stirred overnight. The solution was concentrated *in vacuo*. The residue was purified by chromatography, eluting with 1% triethylamine/dichloromethane to give a triethylamine salt of the title compound (357mg, 79%). MS (ESI⁺) *m/z* 470 (M-H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 0.22 (m, 2 H) 0.46 (br

d, $J=7.35$ Hz, 2 H) 1.01 (m, 1 H) 4.52 (s, 2 H) 5.98 (t, $J=6.62$ Hz, 1 H) 7.24 (s, 1 H) 7.40 (m, 1 H) 7.56 (m, 1 H) 8.05 (m, 1 H).

Example 353E

3-[7-(aminomethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

To the solution of the product of Example 353D (357 mg, 0.62 mmol) in pyridine (4.6 mL) and concentrated ammonium hydroxide (3 mL) was added triphenylphosphine (397 mg, 1.51 mmol) at room temperature. The solution was stirred at room temperature overnight and concentrated under reduced pressure. The residue was diluted with 30% hexane/toluene and the solid was filtered to give the title compound (250 mg, 90%). MS (ESI⁺) m/z 446 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d_6) δ 0.21 (m, 2 H) 0.46 (br d, $J=8.09$ Hz, 2 H) 1.00 (m, 1 H) 4.12 (s, 2 H) 5.98 (t, $J=6.43$ Hz, 1 H) 7.12 (m, 1 H) 7.22 (s, 1 H) 7.58 (m, 1 H) 7.72 (d, $J=7.72$ Hz, 1 H) 8.04 (m, 1 H).

Example 353F

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl)methyl]methanesulfonamide

To the suspension of the triethylamine salt of the product of Example 353E (85.26 mg, 0.16 mmol) in N,N-dimethylformamide (1.6 mL) was added triethylamine (48 μ L, 0.34 mmol) and then methanesulfonyl chloride (13.3 μ L, 0.17 mmol) at room temperature. The solution was stirred at room temperature for 20 minutes and concentrated *in vacuo*. The residue purified by reverse phase chromatography, eluting with 20% to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (39.86 mg, 49%). MS (ESI⁺) m/z 524 (M+H)⁺. ¹H NMR (300 MHz, DMSO- d_6) δ 0.15 (m, 2 H) 0.42 (m, 2 H) 1.01 (m, 1 H) 2.84 (d, $J=7.35$ Hz, 2 H) 2.99 (s, 3 H) 4.29 (d, $J=6.25$ Hz, 2 H) 6.37 (br s, 1 H) 7.41 (m, 2 H) 7.75 (t, $J=6.25$ Hz, 1 H) 7.87 (m, 1 H) 8.08 (d, $J=8.09$ Hz, 1 H) 8.16 (m, 1 H) 14.46 (m, 1 H).

Example 354

3-(8-amino-7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product of Example 321C (0.26 g, 0.61 mmol) in concentrated sulfuric acid (4 mL) at 0°C was treated with ammonium nitrate (55 mg, 0.69 mmol). After stirring at room temperature for 30 minutes, the solution was poured into ice water and the precipitate was filtered, dried, and triturated with ethyl acetate to yield to nitrated intermediate (0.23 g, 79%). A solution of this solid (0.23 g, 0.48 mmol) in methanol:tetrahydrofuran:water (3:3:1) (2.3 mL) was treated with powdered iron (0.12 g, 2.15 mmol) and ammonium chloride (0.031 g, 0.58 mmol) at 60°C for 1 hour. The warm solution was filtered through diatomaceous earth, rinsed with tetrahydrofuran. The filtrate

was concentrated and the resulting solid was triturated with 1:1 dichloromethane:ethyl acetate to yield the title compound (0.088 g, 42%). MS (ESI) m/z 442 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, J =6.62 Hz, 6 H) 1.92 (m, 1 H) 2.76 (m, 2 H) 5.40 (s, 2 H) 6.34 (m, 1 H) 6.66 (d, J =7.72 Hz, 1 H) 7.00 (d, J =8.46 Hz, 1 H) 7.44 (m, 1 H) 7.94 (m, 2 H) 8.17 (d, J =6.99 Hz, 1 H) 10.12 (s, 1 H) 13.82 (s, 1 H) 15.19 (s, 1 H).

Example 355

3-(1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of Example 354 (0.036 g, 0.081 mmol) in dimethylformamide (2 mL) was treated with trimethyl orthoformate (1 mL) and a catalytic amount of para-toluenesulfonic acid at room temperature for 20 hours. The solvent was removed under a stream of warm nitrogen and the residue was triturated with 1:1 ethyl acetate:tetrahydrofuran, filtered, and dried to yield the title compound (8 mg, 22%). MS (ESI) m/z 452 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (d, J =6.62 Hz, 6 H) 1.93 (m, 1 H) 2.78 (m, 2 H) 6.33 (m, 1 H) 7.45 (t, J =7.54 Hz, 1 H) 7.73 (d, J =8.82 Hz, 1 H) 7.92 (t, J =7.72 Hz, 1 H) 8.00 (m, 1 H) 8.21 (m, 2 H) 9.04 (s, 1 H) 14.28 (s, 1 H).

Example 356

2-((8-amino-3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy)acetamide

A solution of the product of Example 321C (0.49 g, 1.15 mmol) in concentrated sulfuric acid (6 mL) at 0°C was treated with ammonium nitrate (100 mg, 1.25 mmol). After stirring at room temperature for 1 hour, the solution was poured into ice water and the precipitate was filtered, dried, and triturated with ethyl acetate to yield nitrated intermediate (0.27 g, 49%). A solution of the nitrated intermediate (75 mg, 0.16 mmol) in N,N-dimethylformamide (3 mL) was treated with 2-bromoacetamide (33 mg, 0.24 mmol) and cesium carbonate (206 mg, 0.63 mmol) in the presence of a catalytic amount of tetrabutylammonium iodide at room temperature for 24 hours. The solvent was removed with a stream of warm nitrogen and the residue was triturated with water, filtered, and dried to yield the alkylated material (76 mg, 90%). A solution of this material in a 3:3:1 mixture of methanol:tetrahydrofuran:water (2.3 mL) was treated with powdered iron (36 mg, 0.64 mmol) and ammonium chloride (9 mg, 0.17 mmol) at 60 °C for 2 hours. The solution was filtered through diatomaceous earth, and rinsed with tetrahydrofuran. The filtrate was concentrated and purified by flash column, eluting with 1% methanol in dichloromethane to yield the title compound (16 mg, 22%). The sodium salt was prepared by the procedure of Example 1D. MS (ESI) m/z 499 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.03 (d, J =6.62 Hz, 6 H) 1.86 (m, 1 H) 2.55 (m, 2 H) 4.39 (s, 2 H) 5.73 (s, 2 H) 5.93 (t, J =7.54 Hz, 1 H) 6.37 (d, J =8.46 Hz, 1 H) 7.04 (m, 2 H) 7.56 (m, 3 H) 7.84 (s, 1 H) 8.06 (d, J =8.46 Hz, 1 H) 15.91

(s, 1 H).

Example 357

3-[8-(chloromethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of Example 354 (0.030 g, 0.067 mmol) in dimethylformamide (3 mL) was treated with 2-chloro-1,1,1-trimethoxyethane (0.50 mL) and a catalytic amount of para-toluenesulfonic acid at 60°C for 4 hours. The solvent was removed under a stream of warm nitrogen and the resulting residue was triturated with water and filtered, then triturated with methanol and filtered to yield the title compound (22 mg, 51%). The sodium salt was made by the procedure of Example 1D. MS (ESI) m/z 500 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, J=6.62 Hz, 6 H) 1.87 (m, J=20.04, 13.42, 6.99 Hz, 1 H) 2.63 (m, 2 H) 5.13 (s, 2 H) 5.95 (t, J=6.99 Hz, 1 H) 7.08 (t, J=7.54 Hz, 1 H) 7.36 (d, J=9.19 Hz, 1 H) 7.57 (m, 2 H) 7.99 (d, J=8.82 Hz, 1 H) 8.09 (dd, J=7.91, 1.29 Hz, 1 H) 16.59 (s, 1 H).

Example 358A

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(propylideneamino)quinolin-2(1H)-one

The product of Example 304F (0.1 g, 0.22 mmol) in N,N-dimethylacetamide (1 mL) was reacted with propionaldehyde diethylacetal (0.34 mL, 2.2 mmol) in a sealed tube in a microwave reactor at 100°C for 60 minutes. The reaction was cooled to 25°C, concentrated under a stream of nitrogen warmed through a manifold heated to 165°C and the resulting residue was triturated with diethyl ether to give the title compound (0.045g, 42 %).

Example 358B

3-[7-(benzyloxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(propylamino)quinolin-2(1H)-one

The product of Example 358A (0.045 g, 0.09 mmol) in tetrahydrofuran (2 mL) at 0°C was treated with methanol (0.005 mL, 0.35 mmol), followed by dropwise addition of a 2.0 M solution of lithium borohydride in tetrahydrofuran (0.07 mL, 0.13 mmol), stirred at 25°C for one hour, and diluted with 1 N hydrochloric acid. The resulting precipitate was filtered and dried. The solid was dissolved in tetrahydrofuran and absorbed onto silica gel by evaporating to dryness. The resulting silica was loaded onto a 2g Alltech sep pack and eluted with dichloromethane to give the title compound (0.020 g, 44 %). MS (ESI) m/z 503 (M-H)⁻.

Example 358C

4-hydroxy-3-(7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(propylamino)quinolin-2(1H)-one

The product of Example 358B (0.020 g, 0.04 mmol) in tetrahydrofuran (5 mL) was treated with ammonium formate (13 mg, 0.19 mmole), palladium hydroxide (2 mg) and 10%

Pd/C (1 mg) and the resulting mixture was refluxed for 1 hour. The catalyst was filtered off and the filtrate evaporated to give a white solid. The solid residue was partitioned between ethyl acetate (100 mL) and water (5 mL). The layers were separated and the organic solvent was removed under reduced pressure to give the title compound (0.016 g, 100%). MS (ESI) m/z 413 (M-H)⁻.

Example 358D

2-({3-[4-hydroxy-2-oxo-1-(propylamino)-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide

The product of Example 358C (0.016 g, 0.04 mmol) in N,N-dimethylformamide (2 mL) was reacted with cesium carbonate (0.015 g, 0.045 mmol), bromoacetamide (0.006 g, 0.18 mmol), and a catalytic amount of tetrabutylammonium iodide at 25°C for 3 hours. The reaction was concentrated under a stream of nitrogen stream of nitrogen warmed through a manifold heated to 165°C and the resulting residue was triturated with water, filtered and dried. The resulting solid was triturated in hot ethyl acetate, filtered, and dried to give the title compound (0.008 g, 37%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI) m/z 470 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (m, 3 H) 1.55 (t, 2 H) 2.73 (t, 2 H) 4.11 (d, 1 H) 4.41 (d, 1 H) 5.83 (d, 1 H) 7.05 (s, 3 H) 7.39 (s, 1 H) 7.54 (s, 2 H) 7.98 (s, 1 H) 16.24 (s, 1 H).

Example 359

3-{3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-8-yl}propanoic acid

A solution of the product of Example 354 (15 mg, 0.033 mmol) and maleic anhydride (100 mg, 1.0 mmol) in pyridine (2 mL) was heated at 160°C in a microwave reactor for 1 hour. The crude mixture was cooled to 25°C and purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (5.3 mg, 30%). The disodium salt was made by the procedure of Example 1D using 2 equivalents of sodium hydroxide. MS (ESI) m/z 524 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.03 (d, J=6.25 Hz, 6 H) 1.86 (m, 1 H) 2.27 (m, 4 H) 2.66 (m, 2 H) 5.94 (t, J=7.54 Hz, 1 H) 6.81 (m, 2 H) 7.05 (t, J=7.91 Hz, 1 H) 7.53 (m, 2 H) 8.06 (d, J=6.62 Hz, 1 H) 15.74 (s, 1 H).

Example 360

3-(8-{[(2-aminoethyl)amino]methyl}-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product from Example 357 (20 mg, 0.039 mmol) and tert-butyl-N-(2-aminoethyl)carbamate (7.7 mg, 0.046 mmol) in N,N-dimethylformamide (3 mL) was treated with cesium carbonate (39 mg, 0.117 mmol) at 50°C for 2 hours. The solvent was removed with a stream of warm nitrogen and the resulting residue was triturated with water,

filtered and dried. This solid was suspended in 1,4-dioxane (2 mL) and treated with a 4M solution of hydrochloric acid in 1,4-dioxane (2 mL) and stirred at room temperature for 20 hours. The solution was concentrated by half, filtered, and dried to yield the dihydrochloride salt of the title compound (5.8 mg, (24%). MS (ESI) m/z 524 (M-H)⁻. ¹H NMR (500 MHz, benzene-d₆) δ 1.05 (d, $J=6.71$ Hz, 6 H) 1.93 (m, 1 H) 2.60 (m, 2 H) 2.81 (d, $J=6.10$ Hz, 2 H) 3.61 (m, 2 H) 4.67 (s, 2 H) 6.17 (m, 1 H) 7.05 (d, $J=9.16$ Hz, 1 H) 7.20 (d, $J=8.54$ Hz, 1 H) 7.44 (t, $J=7.63$ Hz, 1 H) 7.90 (m, 1 H) 7.99 (m, 2 H) 8.17 (d, $J=7.93$ Hz, 1 H) 8.24 (m, 2 H) 13.76 (s, 1 H).

Example 361

2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)propanamide

To a solution of the product of Example 321C (20 mg, 0.0467 mmol) in N,N-dimethylformamide (2 mL) was added 2-bromopropionamide (10.6 mg, 0.070 mmol), *tetra-n*-butylammonium iodide (1.7 mg, 0.0047 mmol) and cesium carbonate (61 mg, 0.187 mmol). The mixture was stirred at 25°C for 72 hours. To the solution was then treated with 1N aqueous hydrochloric acid (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (18.4 mg, 79%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI) m/z 498 (M-Na)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.03 (d, $J = 6.6$ Hz, 6H), 1.45 (d, $J = 6.6$ Hz, 3H), 1.86 (m, 1H), 2.50 (m, 1H), 2.75 (m, 1H), 4.65 (q, $J = 6.6$ Hz, 1H), 5.94 (t, $J = 7.3$ Hz, 1H), 7.08 (m, 2H), 7.17 (m, 1H), 7.23 (m, 1H), 7.29 (s, 1H), 7.58 (m, 2H), 7.64 (s, 1H), 8.07 (d, $J = 6.6$ Hz, 1H), 16.22 (s, 1H).

Example 362

2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)butanamide

To a solution of the product of Example 321C (20 mg, 0.0467 mmol) in N,N-dimethylformamide (2 mL) was added 2-chlorobutyramide (8.5 mg, 0.070 mmol), *tetra-n*-butylammonium iodide (1.7 mg, 0.0047 mmol) and cesium carbonate (61 mg, 0.187 mmol). The mixture was stirred at 25°C for 18 hours, then heated to 80°C for 3 hours. After cooling to 25°C, 1N aqueous hydrochloric acid (10 mL) was added and the mixture extracted with ethyl acetate (10 mL). The resulting organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (24 mg, 100%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. MS (ESI) m/z 512 (M-Na)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (t, $J = 7.7$ Hz, 3H), 1.03 (d, $J = 6.3$ Hz, 6H), 1.83 (m, 3H), 2.50 (m, 1H), 2.75 (m, 1H), 4.46 (m, 1H), 5.94 (m, 1H), 7.08 (m, 2H), 7.17 (m, 1H), 7.23 (m, 1H), 7.32 (s, 1H), 7.58 (m, 2H), 7.64 (s, 1H),

8.07 (d, $J = 7.8\text{ Hz}$, 1H), 16.23 (bs, 1H).

Example 363

methyl {3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-8-yl} acetate

A solution of the product of Example 354 (67.5 mg, 0.015 mmol) in N,N-dimethylformamide (2 mL) was treated with *p*-toluenesulfonic acid monohydrate (1 mg) and monoorthomalonic acid tetramethyl ester (272 mg, 1.52 mmol). The mixture was heated at 50° C in an oil bath under a nitrogen atmosphere and the resulting yellow solution was stirred for 3 hrs. At this time, additional ortho ester was added (272 mg, 1.52 mmol) and heating continued for another 5 hrs. The reaction was cooled to room temperature and the solution was concentrated by rotary evaporation in vacuo. The residue was further dried on a vacuum pump, then dissolved in dichloromethane (100 mL) and washed with water (2 x 50 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 1% methanol/dichloromethane. The resulting impure material was rechromatographed on silica gel, eluting with a gradient of 5% to 7% acetonitrile/dichloromethane to give the title compound (36 mg, 45%). MS (APCI⁺) m/z 526 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (d, $J=6.62\text{ Hz}$, 6 H) 1.91 (m, 1 H) 2.77 (br m, 2 H) 3.72 (s, 3 H) 4.40 (s, 2 H) 6.36 (br m, 1 H) 7.45 (t, $J=7.35\text{ Hz}$, 1 H) 7.70 (d, $J=9.19\text{ Hz}$, 1 H) 7.94 (m, 2 H) 8.20 (d, $J=8.82\text{ Hz}$, 2 H) 14.25 (br s, 1 H). A suspension of the product of Example 363 (6.0 mg, 0.0114 mmol) in anhydrous tetrahydrofuran (3 mL) and distilled water (1 mL) was treated with 0.998 N aqueous sodium hydroxide (0.0114 mL, 0.0114 mmol) and the yellow solution mixed for 15 minutes. The solvent was removed under reduced pressure and the residue dried on a vacuum pump to afford the sodium salt of Example 363 (6.1 mg, 98%). ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, $J=5.15\text{ Hz}$, 6 H) 1.88 (m, 1 H) 2.75 (m, 1 H) 3.72 (s, 3 H) 4.31 (s, 2 H) 5.95 (m, 1 H) 7.08 (m, 1 H) 7.30 (m, 1 H) 7.58 (m, 2 H) 7.95 (m, 1 H) 8.09 (m, 1 H) 16.55 (s, 1 H).

Example 364

4-hydroxy-3-(8-{[3-hydroxypyrrolidin-1-yl]methyl}-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product from Example 357 (80 mg, 0.160 mmol) and 3-hydroxy pyrrolidine (20 mg, 0.240 mmol) in acetonitrile (4 mL) was treated with diisopropylethyl amine (0.115 mL, 0.640 mmol) at room temperature for 24 hours. The solvent was removed under a stream of with warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7 μ m particle size) using a gradient of 10%

to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (16.2 mg, 18%). The sodium salt was made by the procedure of Example 1D. MS (ESI) m/z 551 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d_6) δ 1.04 (d, J=6.62 Hz, 6 H) 1.58 (m, 1 H) 1.88 (m, 1 H) 2.03 (m, 1 H) 2.60 (m, 2 H) 2.75 (m, 2 H) 2.88 (m, J=9.56, 6.25 Hz, 2 H) 3.97 (s, 2 H) 4.23 (m, 1 H) 4.76 (m, 1 H) 5.95 (t, J=7.35 Hz, 1 H) 7.08 (m, 1 H) 7.27 (d, J=8.82 Hz, 1 H) 7.56 (m, 2 H) 7.92 (d, J=8.82 Hz, 1 H) 8.09 (d, J=6.62 Hz, 1 H) 16.51 (s, 1 H).

Example 365

3-[1,1-dioxido-8-(pyridinium-1-ylmethyl)-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-4-olate

A solution of the product of Example 357 (16.5 mg, 0.033 mmol) in pyridine (2 mL) was heated at 45°C for 20 hours. The excess pyridine was removed with a stream of warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (6 mg, 34%). MS (ESI) m/z 543 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d_6) δ 1.03 (d, J=6.62 Hz, 6 H) 1.84 (m, J=13.42, 6.43 Hz, 1 H) 2.72 (m, 2 H) 5.93 (t, J=7.35 Hz, 1 H) 6.39 (s, 2 H) 7.07 (m, 1 H) 7.36 (d, J=8.82 Hz, 1 H) 7.56 (m, 2 H) 8.00 (d, J=8.82 Hz, 1 H) 8.08 (m, 1 H) 8.33 (m, 2 H) 8.78 (t, J=7.91 Hz, 1 H) 9.30 (d, J=5.52 Hz, 2 H) 16.59 (s, 1 H).

Example 366

3-[1,1-dioxido-8-(pyrrolidin-1-ylmethyl)-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product from Example 357 (80 mg, 0.160 mmol) and pyrrolidine (17 mg, 0.240 mmol) in acetonitrile (4 mL) was treated with diisopropylethyl amine (0.115 mL, 0.640 mmol) at ambient temperature for 24 hours. The solvent was removed under a stream of warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (12.4 mg, 15%). The sodium salt was made by the procedure of Example 1D. MS (ESI) m/z 535 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d_6) δ 1.04 (d, J=6.62 Hz, 6 H) 1.73 (m, 4 H) 1.87 (m, 1 H) 2.63 (q, J=4.90 Hz, 4 H) 2.75 (m, 2 H) 3.99 (s, 2 H) 5.95 (t, J=7.35 Hz, 1 H) 7.08 (m, 1 H) 7.27 (d, J=8.82 Hz, 1 H) 7.56 (m, 2 H) 7.92 (d, J=8.82 Hz, 1 H) 8.09 (dd, J=7.90, 1.29 Hz, 1 H) 16.50 (s, 1 H).

Example 367

8-amino-3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-

1,2,4-benzothiadiazin-7-yl methanesulfonate

A solution of the product of Example 354 (44 mg, 0.099 mmol) and methane sulfonyl chloride (0.010 mL, 0.011 mmol) in tetrahydrofuran (4 mL) was treated with diisopropylethylamine (0.075 mL, 0.040 mmol) at room temperature for 2 hours. The solution was poured into water. The resulting precipitate was filtered, dried, and purified by flash column, eluting with 1% methanol in dichloromethane to yield the title compound (14.2 mg, 28%). The sodium salt was made by the procedure of Example 1D. MS (ESI) m/z 520 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.03 (d, J=6.62 Hz, 6 H) 1.88 (m, 1 H) 2.71 (m, 2 H) 3.46 (s, 3 H) 5.94 (m, 1 H) 6.53 (m, 1 H) 7.16 (m, 1 H) 7.35 (m, 1 H) 7.64 (m, 2 H) 8.09 (d, J=7.35 Hz, 1 H) 16.23 (s, 1 H).

Example 3683-[8-(3-aminophenyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A mixture of the product of Example 354 (38 mg, 0.086 mmol) and 3-aminobenzoic acid (13 mg, 0.094 mmol) in polyphosphoric acid (1 mL) was heated to 190°C for 1 hour. The solution was cooled to 25°C, triturated with water and a 10% solution of sodium carbonate. The solid was filtered, dried, and purified by flash column, eluting with 2% methanol in dichloromethane to yield the title compound (15 mg, 38%). The sodium salt was made by the procedure of Example 1D. MS (ESI) m/z 543 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, J=6.62 Hz, 6 H) 1.86 (m, 1 H) 2.56 (m, 2 H) 5.53 (s, 2 H) 5.96 (t, J=7.35 Hz, 1 H) 6.82 (ddd, J=8.09, 2.21, 1.10 Hz, 1 H) 7.08 (td, J=7.35, 1.47 Hz, 1 H) 7.27 (m, 2 H) 7.36 (dt, J=7.72, 1.29 Hz, 1 H) 7.57 (m, 3 H) 7.96 (d, J=8.82 Hz, 1 H) 8.10 (dd, J=8.09, 1.47 Hz, 1 H) 16.51 (s, 1 H).

Example 3693-[8-(aminomethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product of Example 357 (32 mg, 0.063 mmol) in tetrahydrofuran (2 mL) was treated with 20% ammonia in methanol (1 mL) and ammonium hydroxide (1 mL) and 1M sodium hydroxide solution (0.063 mL, 0.063 mmol) at room temperature of 16 hours. The mixture was blown dry with warm nitrogen and the resulting residue was partitioned between water and ethyl acetate. The organic layer was concentrated and purified by flash chromatography, eluting with a gradient of 100% dichloromethane to 2% methanol in dichloromethane, to yield the title compound (4 mg, 13%). MS (ESI) m/z 481 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, J=6.62 Hz, 6 H) 1.91 (m, 1 H) 2.75 (m, 2 H) 4.55 (s, 2 H) 6.33 (m, 1 H) 6.98 (d, J=7.72 Hz, 1 H) 7.16 (d, J=8.46 Hz, 1 H) 7.44 (m, 1 H) 7.92 (m, 2

H) 8.17 (d, J=8.09 Hz, 1 H) 13.65 (s, 1 H) 15.60 (s, 1 H).

Example 370

4-hydroxy-3-[8-(hydroxymethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product of Example 357 (32 mg, 0.063 mmol) in tetrahydrofuran (2 mL) was treated with 20% ammonia in methanol (1 mL) and ammonium hydroxide (1 mL) and 1M sodium hydroxide solution (0.063 mL, 0.063 mmol) at ambient temperature of 16 hours. The mixture was blown dry with warm nitrogen and the resulting residue was partitioned between water and ethyl acetate. The aqueous layer was adjusted to pH 1 with 1M hydrochloric acid and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to yield the title compound (5 mg, 16%). MS (ESI) m/z 482 (M-H). ¹H NMR (300 MHz, DMSO-d₆) δ 1.04 (d, J=6.62 Hz, 6 H) 1.91 (m, 1 H) 2.76 (m, 2 H) 4.82 (s, 2 H) 6.34 (d, J=8.82 Hz, 1 H) 7.31 (d, J=8.82 Hz, 1 H) 7.43 (m, 2 H) 7.92 (m, 2 H) 8.18 (d, J=7.72 Hz, 1 H) 9.04 (s, 1 H) 14.31 (s, 1 H).

Example 371

3-[8-[(butylamino)methyl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product of Example 357 (15.5 mg, 0.031 mmol) in pyridine (2 mL) was treated with n-butyl amine (0.030 mL, 0.31 mmol) at room temperature for 4 hours. The solvent was removed under a stream of warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (1.2 mg, 7.2%). MS (ESI) m/z 537 (M-H). ¹H NMR (300 MHz, DMSO-d₆) δ 0.91 (t, J=7.35 Hz, 3 H) 1.04 (d, J=6.62 Hz, 6 H) 1.36 (m, 2 H) 1.64 (m, 2 H) 1.87 (m, 1 H) 2.66 (m, 2 H) 3.05 (m, 2 H) 4.62 (s, 2 H) 5.96 (t, J=7.54 Hz, 1 H) 7.10 (t, J=6.80 Hz, 1 H) 7.39 (d, J=9.19 Hz, 1 H) 7.59 (m, 2 H) 8.02 (d, J=8.82 Hz, 1 H) 8.09 (d, J=8.09 Hz, 1 H) 16.54 (s, 1 H).

Example 372 RZ

N-[3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]acetamide

To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.5 mL) was added acetic anhydride (0.057 g, 0.0053 mL, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 30 minutes. The reaction was poured into 30 mL of water. The solid was collected by filtration to give the title compound (15.8 mg, 72%). ¹H

NMR (300 MHz, DMSO- d_6) δ 0.98 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.70 (m, 1 H) 2.10 (s, 3 H) 4.48 (m, 2 H) 7.48 (dd, J=8.09, 4.78 Hz, 1 H) 7.66 (d, J=8.82 Hz, 1 H) 7.78 (m, 1 H) 8.30 (d, J=1.84 Hz, 1 H) 8.55 (dd, J=7.72, 1.84 Hz, 1 H) 8.87 (dd, J=4.60, 1.65 Hz, 1 H) 10.39 (s, 1 H) 14.21 (br s, 1 H). MS (ESI) m/z 468 (M-H)⁻.

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Example 373

2,2,2-trifluoro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}acetamide

To a slurry of the product of Example 205 (0.043 g, 0.1 mmol) in 5 mL chloroform was added dropwise, trifluoroacetic anhydride (0.074 g, 0.35 mmol). The reaction mixture was stirred for 30 minutes and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (0.048 g, 92% yield). MS (ESI) m/z 522 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d_6) δ 0.96 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.65 (m, 1 H) 4.30 (m, 2 H) 7.14 (dd, J=7.54, 4.60 Hz, 1 H) 7.35 (d, J=8.82 Hz, 1 H) 7.83 (dd, J=8.82, 2.57 Hz, 1 H) 8.07 (d, J=2.57 Hz, 1 H) 8.37 (dd, J=7.72, 1.84 Hz, 1 H) 8.54 (dd, J=4.78, 1.84 Hz, 1 H) 11.43 (s, 1 H) 16.09 (s, 1 H).

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Example 374

2,2,2-trifluoro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}acetamide

To a solution of trifluoroacetic acid (2.5 mL) and trifluoroacetic anhydride (2.5 mL) at 0°C was added portion wise the product of Example 205 (0.5 g, 1.17 mmol). The resulting red solution was stirred at 0°C for 30 minutes, cooled to -20°C and treated portion wise with potassium nitrate (0.13 g, 1.3 mmol). The mixture was stirred at -20°C for 1 hour, poured onto ice and the resulting tan solid was collected by filtration, washed with water and dried to constant mass to give the title compound (0.628 g, 94% yield). MS (ESI) m/z 567 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO- d_6) δ 0.96 (d, J=6.62 Hz, 6 H) 1.49 (m, 2 H) 1.64 (m, 1 H) 4.30 (m, 2 H) 7.16 (dd, J=7.72, 4.78 Hz, 1 H) 7.67 (m, 2 H) 8.38 (dd, J=7.54, 2.02 Hz, 1 H) 8.57 (dd, J=4.41, 1.84 Hz, 1 H) 11.61 (s, 1 H) 16.67 (s, 1 H).

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Example 375

3-[1,1-dioxido-8-(trifluoromethyl)-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 374 (0.043 g, 0.075 mmol) and iron dust (0.025

g, 0.45 mmol) in acetic acid (2 mL) was heated at 80°C for 1 hour, cooled, diluted with 20 mL ethyl acetate and filtered through a plug of Celite®. The ethyl acetate filtrate was washed with water, brine, dried over sodium sulfate, filtered and concentrated to give the title compound as an orange solid (0.035 g, 90% yield). MS (ESI) m/z 519 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.25 Hz, 6 H) 1.48 (m, 2 H) 1.66 (m, 1 H) 4.31 (m, 2 H) 7.14 (m, 1 H) 7.25 (d, J=8.46 Hz, 1 H) 7.96 (d, J=9.19 Hz, 1 H) 8.38 (d, J=6.99 Hz, 1 H) 8.54 (m, 1 H) 14.46 (s, 1 H) 16.33 (s, 1 H).

Example 376

3-(7-amino-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 374 (0.500 g, 0.88 mmol) and potassium carbonate (1.4 g, 10.1 mmol) in methanol (20 mL), tetrahydrofuran (8 mL) and water (8 mL) was heated at 60°C for 4 hours, cooled and concentrated. The resulting residue was dissolved in ethyl acetate, treated with 1M hydrochloric acid to a pH of about 1, washed with brine, dried over sodium sulfate, filtered and concentrated to give the title compound as a brown solid (0.4 g, 96% yield). MS (ESI) m/z 471 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.96 (d, J=6.62 Hz, 6 H) 1.45 (m, 2 H) 1.64 (m, 1 H) 4.28 (m, 2 H) 6.37 (s, 2 H) 7.13 (dd, J=7.17, 4.23 Hz, 1 H) 7.16 (d, J=9.19 Hz, 1 H) 7.33 (d, J=9.19 Hz, 1 H) 8.35 (dd, J=7.72, 1.84 Hz, 1 H) 8.53 (dd, J=4.78, 1.84 Hz, 1 H) 16.02 (s, 1 H).

Example 377

3-(7,8-diamino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 376 (2.1 g, 4.45 mmol), iron powder (1.24 g, 22.25 mmol) and ammonium chloride (0.29 g, 5.3 mmol) in methanol (50 mL), tetrahydrofuran (50 mL) and water (20 mL) was heated at 75°C for 6 hours, cooled and filtered through a plug of Celite®. The filtrate was treated with 1M hydrochloric acid to a pH of about 2 and the solution was concentrated under vacuum. The resulting residue was stirred in 100 mL of water for 30 minutes and filtered to collect a solid which was then triturated with 50 mL of diethyl ether, filtered and dried to give the title compound (1.72 g, 87% yield). MS (ESI) m/z 441 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.96 (d, J=6.62 Hz, 6 H) 1.49 (m, 2 H) 1.63 (m, 1 H) 4.28 (m, 2 H) 4.63 (s, 2 H) 5.20 (s, 2 H) 6.30 (d, J=8.09 Hz, 1 H) 6.74 (d, J=8.46 Hz, 1 H) 7.10 (dd, J=7.72, 4.78 Hz, 1 H) 8.34 (dd, J=7.72,

1.84 Hz, 1 H) 8.50 (dd, J=4.60, 2.02 Hz, 1 H) 15.41 (s, 1 H).

Example 378

4-hydroxy-3-(8-hydroxy-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl)-
5 1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 377 (0.022 g, 0.05 mmol) and urea (0.012 g, 0.2 mmol) in N,N-dimethylacetamide (0.5 mL) in a sealed tube was heated by microwave at 180°C for 60 minutes. The mixture was cooled and partitioned between ethyl acetate and water adjusted to pH 3 with 1 M hydrochloric acid. The ethyl acetate layer was washed with
10 water, brine, dried over sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting first with dichloromethane and then 96:4 dichloromethane/methanol to give the title compound (0.022 g, 90% yield). MS (ESI⁺) m/z 467 (M-H)⁺. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.62 Hz, 6 H) 1.49 (m, 2 H)
15 1.65 (m, 1 H) 4.29 (m, 2 H) 6.69 (br. s, 1 H) 7.00 (br. s., 1 H) 7.12 (dd, J=7.72, 4.78 Hz, 1 H) 8.36 (m, 1 H) 8.51 (dd, J=4.41, 1.84 Hz, 1 H) 10.66 (s, 1 H) 15.76 (s, 1 H).

Example 379

4-hydroxy-1-(3-methylbutyl)-3-(8-methyl-1,1-dioxido-4,7-dihydroimidazo[4,5-
20 h][1,2,4]benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 377 (0.022 g, 0.05 mmol) and acetic acid (1mL) in a sealed tube was heated by microwave at 160°C for 30 minutes, cooled and filtered to collect a solid which was washed repeatedly with diethyl ether and dried to give the title compound as a tan solid (0.006 g, 26 % yield). MS (ESI⁺) m/z 465 (M-H)⁺. The sodium salt
25 of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.62 Hz, 6 H) 1.48 (m, 2 H) 1.64 (m, 1 H) 2.47 (s, 3 H) 4.31 (m, 2 H) 6.98 (d, J=8.46 Hz, 1 H) 7.13 (dd, J=7.54, 4.96 Hz, 1 H) 7.67 (d, J=8.46 Hz, 1 H) 8.38 (dd, J=7.54, 2.02 Hz, 1 H) 8.53 (dd, J=4.60, 1.65 Hz, 1 H) 12.57 (s, 1 H) 16.04 (s, 1H).

Example 380

3-[1,1-dioxido-8-(pentafluoroethyl)-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl]-
30 4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 377 (0.022 g, 0.05 mmol) and
35 pentafluoropropionic acid (0.5 mL) in a sealed tube was heated by microwave at 130°C for 30 minutes, cooled and concentrated under reduced pressure. The crude material was chromatographed on silica eluting first with dichloromethane and then 99:1

dichloromethane/methanol to give the title compound (0.011 g, 38 % yield). MS (ESI) m/z 569 (M-H)⁻. The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.25 Hz, 6 H) 1.52 (m, 2 H) 1.69 (m, 1 H) 4.37 (m, 2 H) 7.30 (m, 2 H) 7.97 (m, 1 H) 8.54 (m, 2 H) 14.65 (m, 1 H).

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Example 381

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-(7-hydroxy-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one

A solution of the product of Example 320C (47 mg, 0.11 mmol) in concentrated sulfuric acid (2 mL) at 0°C was treated with ammonium nitrate (10 mg, 0.13 mmol). After stirring at ambient temperature for 25 minutes, the solution was poured into ice water and the precipitate was filtered, dried, and purified by flash chromatography, eluting with 2% methanol in dichloromethane to yield the title compound (10 mg, 19%).

MS (ESI) m/z 470 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=4.04 Hz, 2 H) 0.41 (m, 2 H) 1.01 (m, 1 H) 2.84 (d, J=6.99 Hz, 2 H) 7.44 (m, 2 H) 7.77 (d, J=9.56 Hz, 1 H) 7.88 (t, J=7.91 Hz, 1 H) 8.08 (d, J=8.46 Hz, 1 H) 8.16 (dd, J=8.09, 1.10 Hz, 1 H) 11.83 (s, 1 H).

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Example 382

3-(7-{2-[(3S)-3-aminopyrrolidin-1-yl]-2-oxoethoxy}-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

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A mixture of the product of Example 384, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole in N,N-dimethylformamide is added pyrrolidin-3(S)-yl-carbamic acid tert-butyl ester. The mixture is stirred for 1 day. The solution is poured into ethyl acetate and washed with saturated sodium bicarbonate, water, brine and dried with magnesium sulfate. The solvent is removed by vacuo. The residue is triturated with methanol / water and filtered. The solid is added in hydrochloric acid (1 M in dioxane, 2 mL) and stirred overnight, filtered and washed with ethyl acetate/hexane (1:1) to give title compound.

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Example 3832-[3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]-N-ethylacetamide The product of Example 384 (24 mg, 0.05 mmole), 1-[3-(dimethylamino)propyl]-3 ethylcarbodiimide hydrochloride (16 mg, 0.08 mmol) and 1-hydroxybenzotriazole (14 mg, 0.1 mmol) in N,N-dimethylformamide (2 mL) was added ethylamine (100 μ L, 2M in tetrahydrofuran, 0.2 mmol). The mixture was stirred for 1 day. The solution was poured into ethyl acetate (40 mL) and washed with saturated aqueous sodium bicarbonate, water, brine and dried with magnesium sulfate. The solvent was removed under reduced pressure. The residue was

35

trituated with methanol / water and filtered to give title compound (6 mg, 24%). ¹H NMR (500 MHz, DMSO-d₆) δ 0.20 (m, 2 H) 0.45 (m, 2 H) 1.00 (m, 1 H) 1.07 (t, J=7.08 Hz, 3 H) 2.70 (s, 2 H) 3.18 (m, 2 H) 4.49 (s, 2 H) 5.99 (s, br, 1 H) 7.08 (s, br, 1 H) 7.23 (s, br, 3 H) 7.52 (s, br, 1 H) 7.70 (s, br, 1 H) 7.88 (s, br, 1 H) 8.09 (d, J=7.81 Hz, 1 H). MS (ESI) m/z 510 (M-H)⁺.

Example 384A tert-butyl [(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetate The product of Example 320C (400 mg, 0.94 mmol) in N,N-dimethylformamide (10 mL) was reacted with *tert*-butyl bromoacetate (0.555 mL, 3.76 mmol), potassium carbonate (1.225 g, 3.76 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for overnight. The reaction mixture was diluted with water and adjusted to pH 7 with glacial acetic acid. The reaction was extracted with ethyl acetate and the organic layer was washed with aqueous sodium bicarbonate, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel eluting with a gradient of 3:1 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate to give the title compound (195 mg, 38%).

Example 384B [(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetic acid The product of Example 384A (195 mg, 0.36 mmol) in a mixture of trifluoroacetic acid (5 mL) and dichloromethane (5 mL) was stirred for three hours at 25°C. The solvents were removed under reduced pressure. The residue was trituated with hexanes/ethyl acetate (1:1) and filtered to give title compound (114 mg, 65%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=4.04 Hz, 2 H) 0.41 (d, J=7.35 Hz, 2 H) 1.02 (m, 1 H) 2.86 (d, J=6.25 Hz, 2 H) 4.88 (s, 2H) 6.44 (s, 1 H) 7.39 (m, 3 H) 7.67 (d, J=8.82 Hz, 1 H) 7.89 (m, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.17 (dd, J=1.47 Hz, J=6.62 Hz, 1 H) 13.16 (s, 1 H) 14.07 (s, 1 H) 15.12 (s, 1 H). MS (ESI) m/z 483 (M-H)⁺.

Example 385

3-{7-[2-(3-aminopyrrolidin-1-yl)-2-oxoethoxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

The product of Example 384B (24 mg, 0.05 mmole), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (16 mg, 0.08 mmol) and 1-hydroxybenzotriazole (14 mg, 0.1 mmol) in N,N-dimethylformamide (2 mL) was added pyrrolidin-3-yl-carbamic acid *tert*-butyl ester (19 mg, 0.1 mmol). The mixture was stirred for 1 day. The solution was poured into ethyl acetate (40 mL) and washed with saturated aqueous sodium bicarbonate, water, and brine, dried with magnesium sulfate, filtered and concentrated. The residue was trituated with methanol / water and filtered. The solid was treated with hydrochloric acid (1 M in dioxane, 2 mL) and stirred overnight, filtered and washed with ethyl acetate/hexane (1:1) to

give title compound (15 mg, 51%).

¹H NMR (500 MHz, BENZENE-d₆) δ 0.16 (m, 2 H) 0.43 (m, 2 H) 1.01 (m, 1 H) 2.14 (m, 2 H) 2.29 (m, 1 H) 2.89 (d, J=6.84 Hz, 2 H) 3.36 (m, 2 H) 3.81 (m, 2 H) 4.88 (m, 2 H) 7.42 (m, 3 H) 7.61 (m, 1 H) 7.88 (m, 1 H) 8.09 (d, J=8.30 Hz, 1 H) 8.17 (d, J=8.30 Hz, 1 H) 8.28 (s, 3 H) 13.99 (s, 1 H). MS (ESI) m/z 551 (M-H)⁺.

793695 Example 386 DL2

3-(8-amino-7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

A mixture of the product of Example 381 (10 mg, 0.021 mmol), iron powder (5.9 mg, 0.105 mmol), and ammonium chloride (1.3 mg, 0.024 mmol) in methanol:tetrahydrofuran:water (2:2:1, 2mL) was heated at 60°C for 1 hour. The solution filtered through Celite® and washed with tetrahydrofuran. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate, filtered and washed with water and dried to give title compound (5 mg, 53%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.13 (d, J=3.68 Hz, 2 H) 0.40 (d, J=7.72 Hz, 2 H) 1.02 (m, 1 H) 2.85 (d, J=5.52 Hz, 2 H) 5.40 (s, 2 H) 6.46 (s, 1 H) 6.65 (d, J=8.46 Hz, 1 H) 7.00 (d, J=8.09 Hz, 1 H) 7.45 (t, J=7.35 Hz, 1 H) 7.89 (t, J=7.17 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.17 (d, J=8.82 Hz, 1 H) 10.13 (s, 1 H) 13.82 (s, 1 H) 15.17 (s, 1 H). MS (ESI) m/z 440 (M-H)⁺.

Example 387A

2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetamide

The product of Example 381 (20 mg, 0.042 mmol) in N,N-dimethylformamide (2 mL) was treated with 2-bromoacetamide (11.6 mg, 0.084 mmol), potassium carbonate (54.7 mg, 0.168 mmol) and tetrabutylammonium iodide (catalytic) at 25°C, stirred at 25°C for 18 hours. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate, filtered and washed with water to give the title compound (12 mg, 54%).

A mixture of the product of Example 387A (12 mg, 0.023 mmol), iron powder (6.0 mg, 0.107 mmol), and ammonium chloride (1.4 mg, 0.026 mmol) in methanol:tetrahydrofuran:water (2:2:1, 2mL) was heated at 60°C for 1 hour. The solution filtered through Celite® and washed with tetrahydrofuran. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate, filtered washed with water and dried to give title compound (7 mg, 62%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=3.31 Hz, 2 H) 0.41 (d, J=6.99 Hz, 2 H) 1.01 (m, 1 H) 2.85 (d, J=5.88 Hz, 2 H) 4.49 (s, 2 H) 5.98 (s, 2 H) 6.46 (s, 1 H) 6.73 (d, J=8.46 Hz, 1 H) 7.17 (d, J=8.46 Hz, 1 H) 7.44 (t,

J=7.54 Hz, 1 H) 7.55 (s, 1 H) 7.89 (t, J=8.07, 1 H) 7.92 (s, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.16 (d, J=8.09 Hz, 1 H) 13.86 (s, 1 H) 15.07 (s, 1 H). MS (ESI) m/z 497 (M-H)⁺.

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Example 388A

[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetonitrile

10 The product of Example 381 (20 mg, 0.042 mmol) in N,N-dimethylformamide (2 mL) was reacted with 2-bromoacetonitrile (6 μ l, 0.086 mmol), potassium carbonate (54.7 mg, 0.168 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 18 hours. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate, filtered and washed with water to give the title compound (13 mg, 60%).

Example 388B

15 [(8-amino-3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetonitrile

A mixture of the product of Example 388A (13 mg, 0.025 mmol), iron powder (6.0 mg, 0.107 mmol), and ammonium chloride (1.5 mg, 0.028 mmol) in methanol:tetrahydrofuran : water (2:2:1, 2mL) was heated at 60°C for 1 hour. The solution
20 filtered through Celite® and washed with tetrahydrofuran. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate, filtered washed with water and dried to give title compound (5 mg, 41%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=1.11 Hz, 2 H) 0.41 (d, J=5.88 Hz, 2 H) 1.01 (m, 1 H) 2.85 (d, J=5.40 Hz, 2 H) 5.23 (s, 2 H) 5.80 (s, 2 H) 6.45 (s, 1 H) 6.83 (d, J=8.46 Hz, 1 H) 7.38 (d, J=8.46 Hz, 1 H) 7.44 (t,
25 J=7.02 Hz, 1 H) 7.90 (t, J=7.02 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.16 (d, J=7.74 Hz, 1 H) 13.93 (s, 1 H) 14.94 (s, 1 H). MS (ESI) m/z 479 (M-H)⁺.

Example 389

30 1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(2-hydroxyethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]quinolin-2(1H)-one

Product of Example 384 (10 mg, 0.021 mmol) in tetrahydrofuran (10 mL) was added borane (0.8 mL, 1M in tetrahydrofuran, 0.8 mmol). The mixture was refluxed for 4 hours. Then poured into ice water (20 mL) and acidified to pH 2 with 1N hydrochloric acid. The solid was filtered and washed with water to give the title compound (5 mg, 51%). ¹H NMR
35 (300 MHz, DMSO-d₆) δ 0.14 (d, J=4.41 Hz, 2 H) 0.41 (d, J=7.72 Hz, 2 H) 1.01 (m, 1 H) 2.86 (d, J=5.52 Hz, 2 H) 3.74 (t, J=4.78 Hz, 2 H) 4.13 (t, J=4.78 Hz, 2 H) 4.89 (s, 1 H) 6.44 (s, 1 H) 7.41 (m, 3 H) 7.65 (d, J=9.84 Hz, 1 H) 7.89 (t, J=7.91 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H)

8.17 (d, J=7.35 Hz, 1 H) 14.05 (s, 1 H) 15.14 (s, 1 H). MS (ESI) m/z 469 (M-H)⁻.

Example 390A

3-{7-[(1-benzyl-1*H*-imidazol-2-yl)methoxy]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl}-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1*H*)-one

Product of Example 320C (20 mg, 0.047 mmol) in N,N-dimethylformamide (1 mL) was heated with 1-benzyl-2-(chloromethyl)-1H-imidazole hydrochloride (23 mg, 0.095 mmol), potassium carbonate (0.061 g, 0.187 mmol) and tetrabutylammonium iodide (catalytic) at 120°C for 2 hours in a microwave reactor. The solution was cooled to 25°C and concentrated. The residue was triturated with ethyl acetate, filtered and washed with water to give title compound (21 mg, 75%).

Example 390B

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(1H-imidazol-2-ylmethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]quinolin-2(1H)-one

Product of Example 390A (16 mg, 0.027 mmol) in N,N-dimethylformamide (1 mL) was added 1,4-cyclodiene (25.5 μ L, 0.27 mmol) and palladium black (16 mg). The mixture was heated at 70°C for 1 day. The mixture was filtered with Celite® and washed with N,N-dimethylformamide. The solution was evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with dichloromethane:methanol (98:2) to give the title compound (6 mg, 44%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.16 (d, J=4.41 Hz, 2 H) 0.43 (d, J=7.35 Hz, 2 H) 0.99 (m, 1 H) 2.78 (s, br, 2 H) 5.25 (s, 2 H) 6.27 (s, br, 1 H) 7.22 (s, 2 H) 7.31 (m, 1 H) 7.39 (dd, J=9.01, 2.76 Hz, 1 H) 7.49 (d, J=2.57 Hz, 1 H) 7.54 (d, J=8.82 Hz, 1 H) 7.77 (m, 1 H) 7.95 (d, J=8.09 Hz, 1 H) 8.13 (dd, J=8.09 Hz, 1.47 Hz, 1 H) 14.83 (s, br, 1 H). MS (ESI⁺) m/z 505 (M-H)⁺.

Example 391A

1,3-thiazol-2-ylmethanol

To thiazole-2-carbaldehyde (113mg, 1mmol) in methanol (10 mL) was added sodium borohydride (41 mg, 1.2 mmol) portion wise at 0°C. The mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and acidified to pH 3 with 1M hydrochloric acid, and extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with saturated aqueous sodium bicarbonate, water, brine, dried over magnesium

sulfate, filtered and concentrated to give the title compound (69 mg, 60%).

Example 391B

2-(chloromethyl)-1,3-thiazole

The product of Example 391A (66 mg, 0.57 mmol) was added dropwise into thionyl chloride (0.2 mL, 2.7 mmol) in dichloromethane (9 mL) keeping the temperature at 25°C. The mixture was refluxed for 2 hours. The solvent was evaporated to give the title compound (quantitative yield).

Example 391C

1-[(cyclopropylmethyl)amino]-3-[1,1-dioxido-7-(1,3-thiazol-2-ylmethoxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one

Product of Example 320C (15 mg, 0.035 mmol) in N,N-dimethylformamide (1 mL) was heated with Example 391B (19 mg, 0.142 mmol), potassium carbonate (68 g, 0.209 mmol) and tetra-butylammonium iodide (catalytic) at 120°C for 2 hours. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate/hexane (1:1), filtered and washed with water to give title compound (17 mg, 92%). ¹H NMR (500 MHz, DMSO-d₆) δ 0.21 (d, J=4.27 Hz, 2 H) 0.46 (d, J=7.32 Hz, 2 H) 0.99 (m, 1 H) 2.67 (s, br, 2 H) 5.49 (s, 2 H) 5.95 (t, J=6.71 Hz, 1 H) 7.04 (m, 1 H) 7.26 (m, 3 H) 7.50 (m, 1 H) 7.66 (d, J=8.54 Hz, 1 H) 7.75 (d, J=3.66 Hz, 1 H) 7.84 (d, J=3.05 Hz, 1 H) 8.07 (dd, J=7.93 Hz, 1.08 Hz, 1 H) 16.19 (s, 1 H). MS (ESI) m/z 522 (M-H)⁺.

Example 392A

[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetonitrile

The product of Example 320C (0.050 g, 0.117 mmol) in N,N-dimethylformamide (2 mL) was reacted with 2-bromoacetonitrile (16 µL, 0.230 mmol), potassium carbonate (0.15 g, 0.46 mmol) and tetrabutylammonium iodide (catalytic) at 25°C for 1 day. The solution was evaporated under reduced pressure and the residue was triturated with ethyl acetate/hexane (1:1), filtered and washed with water to give title compound (52 mg, 95%).

Example 392B

methyl 2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]ethanimidoate

Hydrogen chloride gas was bubbled into a solution of the product of Example 392A

(50 mg, 0.11 mmol) in methanol (10 mL) at 0°C until saturation. The reaction was stirred at room temperature for 3 hours. The solution was evaporated under reduced pressure to give title compound (quantitative yield).

Example 392C

1-[(cyclopropylmethyl)amino]-3-[7-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one

The product of Example of 392B (53 mg, 0.11 mmol) in methanol (10 mL) was added ethane-1,2-diamine (0.2 mL, 3 mmol) and refluxed overnight. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel eluting with 4:1 dichloromethane/methanol to 3:2 dichloromethane/methanol 3:2 to give the title compound (11 mg, 20%). ¹H NMR (500 MHz, DMSO-d₆) δ 0.18 (m, 2 H) 0.45 (m, 2 H) 1.00 (m, 1 H) 2.77 (d, J=6.71 Hz, 2 H) 3.91 (s, 4 H) 5.23 (s, 2 H) 6.11 (s, 1 H) 7.21 (m, 1 H) 7.42 (m, 3 H) 7.66 (m, 1 H) 7.85 (d, J=7.32 Hz, 1 H) 8.12 (d, J=7.93 Hz, 1 H) 10.70 (s, 1 H) 15.29 (s, 1 H). MS (ESI⁺) m/z 509 (M+H)⁺.

Example 393A

2-(bromomethyl)-1,3-thiazole-4-carbonitrile

To a solution of 2-methyl-1-thiazole-4-carbonitrile (248 mg, 2 mmol) in benzene (20 mL) was added N-bromosuccinimide (1.78 g, 10 mmol) and dibenzoyl peroxide (20 mg, 0.08 mmol). The mixture was refluxed for 2 days. The solution was evaporated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic layer was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with 1:1 dichloromethane:hexane to give the title compound (190 mg, 47%).

Example 393B

2-[[[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl})-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]oxy]methyl]-1,3-thiazole-4-carbonitrile

Product of Example 320C (20 mg, 0.047 mmol) in N,N-dimethylformamide (2 mL) was reacted with Example 393A (20 mg, 0.099 mmol), potassium carbonate (0.070 g, 0.215 mmol) and tetrabutylammonium iodide (catalytic) at room temperature for overnight. The solution was concentrated under reduced pressure and the residue was triturated with ethyl acetate/hexane (1:1), filtered and washed with water to give title compound (23 mg, 89%). ¹H NMR (500 MHz, DMSO-d₆) δ 0.22 (m, 2 H) 0.46 (m, 2 H) 1.00 (m, 1 H) 2.69 (m, 2 H) 5.54 (s, 2 H) 5.96 (t, J=6.32 Hz, 1 H) 7.04 (m, 1 H) 7.28 (m, 3 H) 7.49 (m, 1 H) 7.67 (d,

J=8.62 Hz, 1 H) 8.08 (dd, J=8.05 Hz, 1.70 Hz, 1 H) 8.81 (s, 1 H) 16.15 (s, 1 H), MS (ESI) m/z 547 (M-H)⁺.

Example 394

3-[7-(2-aminoethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

A solution of the product of Example 392A (39 mg, 0.084 mmol) in anhydrous tetrahydrofuran (2 mL) was treated with LiBH₄ (1 mL, 2M in tetrahydrofuran, 0.2 mmol), stirred at ambient temperature for 30 minutes, then 18 µl water was added and stirred overnight. The solution was diluted with water (20 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The slurry was filtered and the solvent removed under reduced pressure to give title compound (38 mg, 97%). ¹H NMR (500 MHz, BENZENE-d₆) δ 0.20 (d, J=3.05 Hz, 2 H) 0.46 (d, J=7.32 Hz, 2 H) 1.01 (m, 1 H) 2.74 (s, br, 2 H) 2.86 (m, 2 H) 4.19 (t, J=4.90 Hz, 2 H) 5.21 (s, br, 2 H) 6.04 (s, br, 1 H) 7.15 (s, br, 1 H) 7.24 (s, br, 2 H) 7.32 (s, br, 1 H) 7.59 (s, br, 1 H) 7.78 (s, br, 1 H) 8.11 (d, J=7.32 Hz, 1 H) 15.65 (s, br, 1 H). MS (ESI) m/z 468 (M-H)⁺.

Example 395

N-[2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]ethyl]methanesulfonamide

To the product of Example 394 (15 mg, 0.032 mmol) in pyridine (1 mL) was added methanesulfonyl chloride (12 µl, 0.156 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1 hexane:ethyl acetate. The crude product was purified by chromatography on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (5 mg, 29%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=4.04 Hz, 2 H) 0.41 (d, J=7.72 Hz, 2 H) 1.01 (m, 1 H) 2.86 (d, J=5.52 Hz, 2 H) 2.97 (s, 3 H) 3.38 (t, J=5.33 Hz, 2 H) 4.18 (t, J=5.33 Hz, 2 H) 6.44 (s, 1 H) 7.32 (t, J=5.88 Hz, 1 H) 7.41 (m, 3 H) 7.67 (d, J=9.93 Hz, 1 H) 7.89 (t, J=7.91 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.17 (d, J=8.46 Hz, 1 H) 14.08 (s, 1 H) 15.11 (s, 1 H). MS (ESI) m/z 546 (M-H)⁺.

Example 396

3-[9-(butylamino)-1,1-dioxido-4H,8H-[1,4]oxazino[2,3-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A solution of the product of Example 357 (15.5 mg, 0.031 mmol) in pyridine (2 mL)

was treated with n-butyl amine (0.030 mL, 0.31 mmol) at room temperature for 4 hours. The solvent was removed under a stream of warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic to yield the title compound (3.3 mg, 20%). MS (ESI⁺) m/z 537 (M-H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (t, J=7.35 Hz, 3 H) 1.04 (d, J=6.62 Hz, 6 H) 1.36 (m, 2 H) 1.59 (m, 2 H) 1.90 (m, 1 H) 2.70 (m, 2 H) 3.41 (m, 2 H) 4.55 (s, 2 H) 6.32 (m, 1 H) 6.96 (m, 1 H) 7.15 (d, J=8.46 Hz, 1 H) 7.45 (m, 1 H) 7.93 (m, 2 H) 8.17 (d, J=6.62 Hz, 1 H) 13.66 (s, 1 H) 15.69 (s, 1 H).

Example 3973-[7-[(5-bromopyridin-2-yl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one

A mixture of the product of Example 321C (40.0 mg, 0.09 mmol), cesium carbonate (112 mg, 0.34 mmol), and 2,5-dibromopyridine (40.0 mg, 0.17 mmol) in dimethylsulfoxide (1.2 mL) was stirred while heating at 110°C in a microwave reactor for 20 minutes. After cooling to 25°C, the purple mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with an additional portion of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with a step gradient (0-100%) of dichloromethane in hexanes to give the title compound as an off-white solid (34.0 mg, 63%). MS (ESI⁺) m/z 582 (M-H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 1.05 (d, J=6.62 Hz, 6 H) 1.93 (m, 1 H) 2.73 (m, 2 H) 6.35 (m, 1 H) 7.19 (d, J=8.82 Hz, 1 H) 7.45 (m, 1 H) 7.61 (dd, J=8.82, 2.57 Hz, 1 H) 7.77 (m, 2 H) 7.94 (m, 2 H) 8.13 (dd, J=8.82, 2.57 Hz, 1 H) 8.19 (m, 1 H) 8.31 (d, J=2.21 Hz, 1 H).

Example 398

4-hydroxy-1-(isobutylamino)-3-[7-[(3-nitropyridin-2-yl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]quinolin-2(1H)-one

A mixture the product of Example 321C (10.0 mg, 0.02 mmol), cesium carbonate (27.7 mg, 0.09 mmol), and 2-bromo-3-nitropyridine (8.4 mg, 0.04 mmol) in dimethylsulfoxide (0.3 mL) was stirred while heating at 110°C in a microwave reactor for 20 minutes. After cooling to 25°C, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with an additional portion of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with a 0-100% dichloromethane in hexane step gradient to give the title compound as a yellow solid (8.6 mg, 68%). MS (ESI⁺) m/z 549 (M-H)⁺. ¹H NMR (300 MHz, CDCl₃) δ 1.13 (d, J=6.62 Hz, 6 H) 2.00 (m, 1 H) 2.81 (m, 2 H) 5.73 (m, 1 H) 7.23 (m, 1 H) 7.40 (m, 2 H) 7.50 (dd, J=8.82, 2.57 Hz, 1 H) 7.82 (m, 2 H) 7.97 (m, 1 H) 8.27 (dd, J=8.09, 1.10 Hz, 1 H) 8.35 (dd, J=4.78, 1.84 Hz, 1 H) 8.42 (dd,

J=8.09, 1.84 Hz, 1 H) 14.39 (s, 1 H) 15.02 (s, 1 H).

Example 399

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.2 mL) was added methanesulfonyl chloride (0.0064 g, 0.0043 mL, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 38 minutes. The reaction was diluted with ethyl acetate (40mL), washed with 1 N hydrochloric acid, water, and brine. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a yellow solid, which was purified by chromatography on silica gel eluting with 99:1 dichloromethane : methanol to give the title compound (8.3 mg, 35%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.70 (m, 1 H) 3.10 (s, 3 H) 4.49 (m, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.58 (dd, J=8.82, 2.57 Hz, 1 H) 7.64 (d, J=2.21 Hz, 1 H) 7.75 (d, J=8.82 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.60, 1.65 Hz, 1 H) 10.29 (s, 1 H) 14.17 (s, 1 H). MS (ESI) m/z 504 (M-H).

Example 400

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}benzenesulfonamide

To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.2 mL) was added benzenesulfonyl chloride (0.0099 g, 0.0072 mL, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 35 minutes. The reaction was cooled to 25°C, diluted with ethyl acetate (40mL), washed with 1 N hydrochloric acid, water, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with 99:1 dichloromethane : methanol to give the title compound (18.6 mg, 69%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.25 Hz, 6 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 4.46 (m, 2 H) 7.47 (m, 3 H) 7.61 (m, 4 H) 7.80 (d, J=6.99 Hz, 2 H) 8.54 (dd, J=7.91, 1.65 Hz, 1 H) 8.87 (dd, J=4.23, 1.29 Hz, 1 H) 10.85 (s, 1 H) 14.08 (br s, 1 H). MS (ESI) m/z 566 (M-H).

Example 401

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}thiophene-2-sulfonamide

To the product of Example 205 (21.5 mg, 0.05mmol) in pyridine (1mL) was added 2-thiophenesulfonyl chloride (44 mg, 0.24 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and

concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with hexane:ethyl acetate (1:1). The crude product was chromatographed on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (10 mg, 35%). ¹H NMR (300 MHz, DMSO-d₆): δ 0.97 (d, J=6.25 Hz, 6 H) 1.55 (m, 2 H) 1.66 (m, 1 H) 4.46 (t, J=7.84 Hz, 2 H) 7.16 (dd, J=5.13 Hz, 3.66 Hz, 1 H) 7.48 (m, 2 H) 7.53 (d, J=2.21 Hz, 1 H) 7.56 (d, J=2.55 Hz, 1 H) 7.61 (dd, J=3.68, 1.47 Hz, 1 H) 7.68 (d, J=8.82 Hz, 1 H) 7.96 (dd, J=5.13 Hz, 1.47 Hz, 1 H) 8.53 (dd, J=8.09, 1.84 Hz, 1 H) 8.87 (dd, J=4.78, 1.84 Hz, 1 H) 10.98 (s, 1 H) 14.10 (s, 1 H). MS (ESI) m/z 572 (M-H)⁺.

Example 402

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-1-methyl-1H-imidazole-4-sulfonamide

To the product of Example 205 (21.5 mg, 0.05 mmol) in pyridine (1mL) was added 1-methylimidazolesulfonyl chloride (44 mg, 0.24 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1hexane:ethyl acetate to give the title compound (21 mg, 73%). ¹H NMR (300 MHz, DMSO-d₆): δ 0.98 (d, J=6.62 Hz, 6 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 3.66 (s, 3 H) 4.48 (m, 2 H) 7.58 (m, 5 H) 7.78 (d, J=1.11 Hz, 1 H) 7.92 (d, J=1.47 Hz, 1 H) 8.55 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.78, 1.84 Hz, 1 H) 10.80 (s, 1 H) 13.99 (s, 1 H). MS (ESI) m/z 570 (M-H)⁺.

Example 403

4,5-dichloro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}thiophene-2-sulfonamide

To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.2 mL) was added 2,3-dichlorothiophene-5-sulfonyl chloride (0.015 g, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 15 minutes. The reaction was diluted with ethyl acetate (40mL), washed with 1 N hydrochloric acid, water, and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with 99:1 dichloromethane:methanol to give the title compound (14.8 mg, 50%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.25 Hz, 6 H) 1.56 (m, 2 H) 1.69 (m, 1 H) 4.47 (m, 2 H) 7.50 (m, 2 H) 7.56 (s, 1 H) 7.71 (d, J=8.82 Hz, 1 H) 7.76 (s, 1 H) 8.55 (dd, J=7.91, 2.02 Hz, 1 H) 8.88 (dd, J=4.60, 1.65 Hz, 1 H) 11.28 (s, 1 H) 14.19 (br s, 1 H). MS (ESI) m/z 640 (M-H)⁺.

Example 4042,2,2-trifluoro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}ethanesulfonamide

To the product of Example 205 (21.5 mg, 0.05 mmol) in pyridine (1 mL) was added
 5 2,2,2-trifluoroethanesulfonyl chloride (28 μ l, 0.25 mmol). The reaction mixture was heated
 in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and
 concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered,
 and washed with of 1:1 hexane:ethyl acetate. The crude product was chromatographed on
 silica gel eluting with 1:1 ethyl acetate/hexane to give the title compound (5 mg, 17%). ¹H
 10 NMR (300 MHz, DMSO-d₆): δ 0.97 (d, J=6.62 Hz, 6 H) 1.49 (m, 2 H) 1.64 (m, 1 H) 4.31 (t,
 J=7.53 Hz, 2 H) 4.58 (q, J=9.93 Hz, 2 H) 7.17 (dd, J=7.35, 4.78 Hz, 1 H) 7.43 (m, 4 H) 8.38
 (dd, J=7.72, 1.84 Hz, 1 H) 8.57 (d, J=2.94 Hz, 1 H) 10.63 (s, 1 H) 15.90 (s, 1 H). MS (ESI)
 m/z 572 (M-H).

Example 405methyl [(3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]acetate

To product of example 205 (21.5 mg, 0.05 mmol) in methylene chloride (1 mL) was
 added chlorosulfonyl-acetic acid methyl ester (35 mg, 0.2 mmol) and triethylamine (30 μ l,
 20 0.22 mmol) and the resulting mixture was stirred at room temperature for 3 days. Upon
 completion of the reaction, the solvent was removed under reduced pressure. The residue
 was chromatographed on silica gel eluting with 199:1 dichloromethane:methanol. The
 product was dissolved in dichloromethane and added two drops of acetic acid, then stirred at
 rt for 10 min, washed with water. The organic layer was dried with magnesium sulfate and
 25 evaporated in vacuo to give the title compound (2 mg, 7%). ¹H NMR (300 MHz, DMSO-
 d₆): δ 0.99 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.70 (m, 1 H) 3.65 (s, 3 H) 4.40 (s, 2 H) 4.49
 (m, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.59 (dd, J=8.82, 2.57 Hz, 1 H) 7.66 (d, J=2.57 Hz,
 1 H) 7.76 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H)
 10.73 (s, 1 H) 14.15 (s, 1 H). MS (ESI) m/z 562 (M-H).

Example 406N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}ethanesulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added
 35 ethanesulfonyl chloride (19 μ l, 0.2 mmol). The reaction mixture was heated in a microwave
 reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under
 reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with

1:1 hexane:ethyl acetate. The crude product was chromatographed on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (3 mg, 11%). ¹H NMR (300 MHz, DMSO-d₆): δ 0.98 (d, J=6.62 Hz, 6 H) 1.22 (t, J=7.35 Hz, 3 H) 1.58 (m, 2 H) 1.70 (m, 1 H) 3.20 (q, J=7.35 Hz, 2 H) 4.49 (m, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.58 (dd, J=8.82, 2.57 Hz, 1 H) 7.65 (d, J=2.57 Hz, 1 H) 7.74 (d, J=9.19 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.60, 1.65 Hz, 1 H) 10.35 (s, 1 H) 14.15 (s, 1 H). MS (ESI⁺) m/z 518 (M-H)⁺.

Example 407

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}propane-2-sulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added isopropylsulfonyl chloride (22 μl, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1 hexane:ethyl acetate. The crude product was chromatographed on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (2 mg, 7%). ¹H NMR (300 MHz, DMSO-d₆): δ 0.98 (d, J=6.62 Hz, 6 H) 1.28 (d, J=6.99 Hz, 6 H) 1.57 (m, 2 H) 1.71 (m, 1 H) 3.29 (m, 1 H) 4.49 (m, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.59 (dd, J=8.82, 2.57 Hz, 1 H) 7.67 (d, J=2.57 Hz, 1 H) 7.74 (d, J=9.18 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.60, 1.65 Hz, 1 H) 10.33 (s, 1 H) 14.11 (s, 1 H). MS (ESI⁺) m/z 532 (M-H)⁺.

Example 408

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-1-phenylmethanesulfonamide

A solution of the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was treated with α-toluenesulfonyl chloride (38 mg, 0.2 mmol), heated in a microwave reactor at 120°C for 120 minutes, cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with hexane:ethyl acetate (1:1). The crude product was chromatographed on silica gel, eluting with dichloromethane:methanol (399:1) to give the title compound (7 mg, 24%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.69 (m, 1 H) 4.49 (m, 2 H) 4.59 (s, 2 H) 7.32 (m, 5 H) 7.51 (m, 2 H) 7.57 (d, J=2.21 Hz, 1 H) 7.71 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.78, 1.84 Hz, 1 H) 10.38 (s, 1 H) 14.08 (s, 1 H) 15.14 (s, 1 H) (ESI⁺) m/z 580 (M-H)⁺.

Example 409A

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]-2-nitrobenzenesulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added 2-nitrobenzenesulfonyl chloride (44 mg, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was concentrated under reduced pressure. The residue was triturated with water (1 ml), filtered, and washed with of hexane:ethyl acetate (1:1). The crude product was chromatographed on silica gel, eluting with dichloromethane:methanol (399:1) to give the title compound (8 mg, 26%).

Example 409B

2-amino-*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]benzenesulfonamide

A mixture of the product of Example 409A (8 mg, 0.013 mmol), iron powder (5.0 mg, 0.089 mmol), and NH₄Cl (1 mg, 0.019 mmol) in methanol:tetrahydrofuran:water (2:2:1, 10 mL) was heated at 60°C for 2 hour. The solution filtered through Celite® and washed with THF. The solution was concentrated and the residue was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, dried with MgSO₄, filtered and concentrated to give title compound (7 mg, 92%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.97 (d, J=6.62 Hz, 6 H) 1.54 (m, 2 H) 1.68 (m, 1 H) 4.46 (m, 2 H) 6.06 (s, 2 H) 6.59 (t, J=7.17 Hz, 1 H) 6.78 (d, J=8.46 Hz, 1 H) 7.23 (m, 1 H) 7.46 (m, 4 H) 7.63 (d, J=8.82 Hz, 1 H) 8.53 (dd, J=8.09, 1.84 Hz, 1 H) 8.87 (dd, J=4.41, 1.84 Hz, 1 H) 10.79 (s, 1 H) 14.00 (s, 1 H). (ESI) m/z 581 (M-H).

Example 410

3-[8-(chloromethyl)-1,1-dioxido-4,7-dihydroimidazo[4,5-*h*][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one

A mixture of the product of Example 377 (0.022 g, 0.05 mmol) and chloroacetic acid (0.06 g, 0.63 mmol) in a sealed tube was heated in a microwave reactor at 120°C for 30 minutes, cooled to 25°C and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with dichloromethane and then 98:2 dichloromethane:methanol to give the title compound (0.010 g, 40 % yield). MS (APCI⁺) m/z 501 (M+H)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.60 (m, 2 H) 1.71 (m, 1 H) 4.50 (m, 2 H) 5.00 (m, 2 H) 7.47 (m, 2 H) 7.95 (d, J=8.09 Hz, 1 H) 8.57 (dd,

J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.47 Hz, 1 H).

Example 411

{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-8-yl} acetonitrile

A mixture of the product of Example 377 (0.044 g, 0.1 mmol) and cyanoacetic acid (0.085 g, 1.0 mmol) in a sealed tube was heated in a microwave reactor at 120°C for 30 minutes, cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give a residue which was chromatographed on silica gel eluting first with dichloromethane and then 98:2 dichloromethane/methanol to give the title compound (0.007 g, 14 % yield). MS (ESI) m/z 490 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.71 (m, 1 H) 4.49 (m, 4 H) 7.50 (m, 2 H) 7.96 (m, 1 H) 8.57 (dd, J=7.72, 1.84 Hz, 1 H) 8.89 (dd, J=4.60, 1.29 Hz, 1 H).

Example 412

methyl {3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-8-yl} acetate

A mixture of the product of Example 377 (0.088 g, 0.2 mmol), 3,3,3-trimethoxypropionic acid methyl ester (0.360 g, 2.0 mmol) and catalytic p-toluenesulfonic acid monohydrate in a sealed tube was heated in a microwave reactor at 60 °C for 30 minutes, cooled to 25°C and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting first with dichloromethane and then 97:3 dichloromethane/methanol to give the title compound (0.051 g, 49 % yield). MS (ESI) m/z 523 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.58 (m, 2 H) 1.71 (m, 1 H) 3.68 (s, 3 H) 4.10 (s, 2 H) 4.49 (m, 2 H) 7.45 (d, J=8.46 Hz, 1 H) 7.51 (dd, J=7.91, 4.60 Hz, 1 H) 7.92 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=7.91, 1.65 Hz, 1 H) 8.90 (dd, J=4.60, 1.65 Hz, 1 H) 13.07 (br. s., 1 H) 14.21 (br. s., 1 H) 15.31 (br. s., 1 H).

Example 413

3-(9,9-dioxido-6H-[1,2,5]thiadiazolo[3,4-h][1,2,4]benzothiadiazin-7-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

A mixture of the product of Example 377 (0.044 g, 0.1 mmol) and sulfamide (0.048 g, 0.5 mmol) in a sealed tube was heated in a microwave reactor at 190°C for 4 minutes, cooled TO 25°C and concentrated. The crude product was purified by chromatography on reverse phase gradient eluting with 0.1% trifluoroacetic acid in water/methanol (90/10) to

0.1% trifluoroacetic in water/methanol (5/95) to give the title compound (0.005 g, 11 % yield). MS (ESI⁺) m/z 469 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.59 (m, 2 H) 1.71 (m, 1 H) 4.49 (m, 2 H) 7.48 (dd, J=7.91, 4.60 Hz, 1 H) 7.93 (d, J=9.56 Hz, 1 H) 8.39 (d, J=9.19 Hz, 1 H) 8.57 (dd, J=7.72, 1.84 Hz, 1 H) 8.88 (dd, J=4.78, 1.84 Hz, 1 H) 14.38 (s, 1 H).

Example 414A

tert-butyl 4-amino-3-(aminosulfonyl)phenylcarbamate

A mixture of 2,5-diaminosulfonamide [prepared according to the procedure of *J. Amer. Chem. Soc.* **1943**, 65, 738] (0.168 g, 0.896 mmol) and di-tert-butyl dicarbonate (0.196 g, 0.896 mmol) in tetrahydrofuran (10 mL) was stirred at room temperature for 16 hours. The reaction was concentrated under reduced pressure and the residue purified by chromatography on silica gel, eluting with 3:2 hexane/ethyl acetate, to provide the title compound (0.202 g, 78% yield).

Example 414B

tert-butyl 3-[1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-ylcarbamate

A mixture of the product of Example 414A (78.1 mg, 0.272 mmol) and the product of Example 353B (91.0 mg, 0.272 mmol) in anhydrous dioxane (2.7 mL) was heated under reflux for 3 h. The reaction mixture was then cooled to 25°C and concentrated under reduced pressure to yield an oily solid. The solid was triturated with methanol to yield the title compound (72.5 mg, 51%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, J=4.04 Hz, 2 H) 0.42 (m, 2 H) 1.00 (m, 1 H) 1.51 (s, 9 H) 2.85 (bd, J=4.78 Hz, 2 H) 6.45 (bs, 1 H) 7.44 (t, J=7.54 Hz, 1 H) 7.62 (d, J=8.82 Hz, 1 H) 7.69 (dd, J=8.82, 2.20 Hz, 1 H) 7.89 (m, J=7.91, 7.91 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.17 (m, 2 H) 9.93 (s, 1 H) 14.08 (s, 1 H) 15.15 (d, J=4.78 Hz, 1 H). MS (ESI⁺) m/z 524.0 (M-H)⁻. The sodium salt of the compound was prepared by reacting example 414B (3.9 mg, 0.0074 mmol) with 1 N sodium hydroxide solution (0.0074 mL, 0.0074 mmol) in 0.5 mL water and 0.5 mL tetrahydrofuran at room temperature for 1.2 h. The reaction mixture was then evaporated under a stream of nitrogen to provide the sodium salt (4.1 mg, 100% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 0.20 (m, J=5.52 Hz, 2 H) 0.46 (d, J=8.82 Hz, 2 H) 1.00 (m, 1 H) 1.50 (s, 9 H) 3.30 (m, 2 H) 5.96 (t, J=6.25 Hz, 1 H) 7.06 (t, J=7.17 Hz, 1 H) 7.20 (d, J=9.19 Hz, 1 H) 7.52 (m, 2 H) 7.67 (d, J=8.82 Hz, 1 H) 7.90 (s, 1 H) 8.06 (d, J=7.35 Hz, 1 H) 9.60 (s, 1 H) 16.22 (s, 1 H). MS (ESI⁺) m/z 543.1 (M+H+H₂O-Na)⁺, 526.1 (M-Na)⁺, (ESI⁻) m/z 524.1 (M-H)⁻.

Example 4153-(7-amino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one

5 A solution of the product of Example 414B (10.1 mg, 0.0192 mmol) in trifluoroacetic acid (0.5 mL) and dichloromethane (0.5 mL) was stirred at room temperature for 15 min. The solvent was then evaporated under a stream of nitrogen to provide the title compound (10.4 mg, quantitative yield.). ¹H NMR (300 MHz, DMSO-d₆) δ 0.13 (d, J=4.04 Hz, 2 H) 0.41 (d, J=6.99 Hz, 2 H) 1.01 (m, 1 H) 2.85 (d, J=6.99 Hz, 2 H) 6.98 (m, 2 H) 7.38 (d, J=8.46 Hz, 1 H) 7.44 (t, J=7.72 Hz, 1 H) 7.89 (m, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 8.16 (d, J=6.99 Hz, 1 H) 13.87 (s, 1 H) 15.40 (s, 1 H). MS (ESI⁺) m/z 426.0 (M+H)⁺, 448.0 (M+Na)⁺, (ESI⁻) m/z 424.1 (M-H)⁻.

Example 416N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-4-(methylsulfonyl)benzenesulfonamide

15 To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.2 mL) was added 4-methylsulfonylbenzenesulfonyl chloride (0.014 g, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 30 minutes. The reaction was cooled to 25°C and diluted with ethyl acetate (40mL), washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with 99:1 dichloromethane:methanol to give the title compound (15 mg, 50%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.25 Hz, 6 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 3.28 (s, 3 H) 4.46 (m, 2 H) 7.48 (m, 3 H) 7.65 (d, J=8.82 Hz, 1 H) 8.04 (d, J=8.82 Hz, 2 H) 8.15 (d, J=8.46 Hz, 2 H) 8.54 (dd, J=8.09, 1.84 Hz, 1 H) 8.86 (dd, J=4.60, 1.65 Hz, 1 H) 11.11 (s, 1 H) 14.14 (s, 1 H). MS (ESI⁻) m/z 644 (M-H)⁻.

Example 417methyl 3-[(3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]thiophene-2-carboxylate

30 To the product of Example 205 (0.020 g, 0.047 mmol) in pyridine (0.2 mL) was added 2-(methoxycarbonyl)thiophene-3-sulfonyl chloride (0.014 g, 0.056 mmol). The reaction mixture was heated in a microwave reactor at 100°C for 30 minutes. The reaction was cooled to 25°C, diluted with ethyl acetate (40mL), washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel eluting with 99:1 dichloromethane/methanol to give the title compound (15 mg, 50%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.25 Hz, 6 H) 1.56

(m, 2 H) 1.69 (m, 1 H) 3.89 (s, 3 H) 4.46 (m, 2 H) 7.50 (m, 4 H) 7.65 (d, J=8.82 Hz, 1 H) 8.01 (d, J=5.15 Hz, 1 H) 8.54 (dd, J=7.91, 1.65 Hz, 1 H) 8.88 (dd, J=4.60, 1.65 Hz, 1 H) 10.74 (s, 1 H) 14.06 (s, 1 H). MS (ESI) m/z 630 (M-H)⁺.

5

Example 418

3-(8-amino-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl)-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 377 (24 mg, 0.055 mmole) was suspended in water (0.1 mL) and cooled to 0°C in an ice bath. To this slurry was added an acetonitrile solution of
10 cyanogen bromide (0.1 mL, 0.067 mmole) and the mixture was stirred for 42 hours at room temperature. The reaction mixture was concentrated under reduced pressure to give the title compound (23.5 mg, 92%). The compound was converted to the sodium salt as described in example 1D. MS (ESI) m/z 466 (M-H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.62 Hz, 6 H) 1.49 (s, 2 H) 1.65 (s, 1 H) 4.29 (d, J=8.46 Hz, 2 H) 6.01 (s, 2 H) 6.49 (s, 1 H) 6.78
15 (d, J=8.09 Hz, 1 H) 7.12 (dd, J=7.72, 4.41 Hz, 1 H) 7.30 (d, J=8.09 Hz, 1 H) 8.38 (m, 1 H) 8.51 (d, J=1.47 Hz, 1 H) 11.03 (s, 1 H).

Example 419

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}propane-1-sulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added 1-propanesulfonyl chloride (22.5 mL, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered,
25 and washed with 1:1 hexane:ethyl acetate. The crude product was chromatographed on reverse phase HPLC eluting with 0.1% aqueous trifluoroacetic acid/methanol (90/10) to 0.1% aqueous trifluoroacetic acid/methanol (5/95) to give the title compound (3 mg, 11%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (m, 9 H) 1.57 (m, 2 H) 1.69 (m, 3 H) 3.17 (t, J=7.74 Hz, 2 H) 4.49 (t, J=7.74 Hz, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.58 (dd, J=8.82, 2.57 Hz, 1 H)
30 7.64 (d, J=2.21 Hz, 1 H) 7.75 (d, J=8.82 Hz, 1 H) 8.56 (dd, J=7.72, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H) 10.35 (s, 1 H) 14.09 (s, 1 H). MS (ESI) m/z 532 (M-H)⁺.

Example 420

2-chloro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}benzenesulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added 2-chlorobenzenesulfonyl chloride (27 mL, 0.2 mmol). The reaction mixture was heated in a

microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1 hexane:ethyl acetate. The crude product was purified by chromatography on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (14 mg, 46%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.96 (d, J=6.25 Hz, 6 H) 1.54 (m, 2 H) 1.67 (m, 1 H) 4.44 (t, J=7.71 Hz, 2 H) 7.57 (m, 7 H) 8.11 (d, J=8.46 Hz, 1 H) 8.52 (dd, J=8.09, 1.84 Hz, 1 H) 8.86 (dd, J=4.78, 1.84 Hz, 1 H) 11.24 (s, 1 H) 13.99 (s, 1 H). MS (ESI) m/z 600 (M-H).

Example 421

1-chloro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added chloromethylsulfonyl chloride (18 mL, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with of 1:1 hexane:ethyl acetate. The crude product was purified by chromatography on reverse phase gradient eluting with 0.1% trifluoroacetic acid in water/methanol (90/10) to 0.1% trifluoroacetic in water/methanol (5/95) to give the title compound (6 mg, 22%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.69 (m, 1 H) 4.49 (t, J=7.74 Hz, 2 H) 5.18 (s, 2 H) 7.51 (dd, J=7.91, 4.60 Hz, 1 H) 7.62 (dd, J=8.82, 2.57 Hz, 1 H) 7.67 (d, J=2.57 Hz, 1 H) 7.77 (d, J=8.82 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H) 10.91 (s, 1 H) 14.10 (s, 1 H). MS (ESI) m/z 538 (M-H).

Example 422

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}butane-1-sulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added 1-butan sulfonyl chloride (26 mL, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1 hexane:ethyl acetate. The crude product was chromatographed on silica gel eluting with 199:1 dichloromethane:methanol to give the title compound (8 mg, 29%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (t, J=7.35 Hz, 3 H) 0.98 (d, J=6.62 Hz, 6 H) 1.37 (m, 2 H) 1.56 (m, 2 H) 1.69 (m, 3 H) 3.19 (t, J=7.74 Hz, 2 H) 4.48 (t, J= 7.74 Hz, 2 H) 7.50 (dd, J=7.91, 4.60 Hz, 1 H) 7.58 (dd, J=9.01, 2.39 Hz, 1 H) 7.65 (d, J=2.21 Hz, 1 H) 7.75 (d,

J=8.82 Hz, 1 H) 8.55 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.41, 1.84 Hz, 1 H) 10.35 (s, 1 H) 14.07 (s, 1 H) 15.13 (s, 1 H). MS (ESI⁺) m/z 548 (M+H)⁺.

Example 423

5 2,6-dichloro-N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}benzenesulfonamide

To the product of Example 205 (21.5g, 0.05 mmol) in pyridine (1 mL) was added 2,6-dichlorobenzenesulfonyl chloride (49, 0.2 mmol). The reaction mixture was heated in a microwave reactor at 120°C for 120 minutes. The reaction was cooled to 25°C and concentrated under reduced pressure. The residue was triturated with water (1 mL), filtered, and washed with 1:1 hexane:ethyl acetat. The crude product was chromatographed on silica gel eluting with 399:1 dichloromethane:methanol to give the title compound (5 mg, 16%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, J=6.62 Hz, 6 H) 1.54 (m, 2 H) 1.67 (m, 1 H) 4.46 (m, 2 H) 7.47 (m, 2 H) 7.58 (m, 2 H) 7.68 (m, 3 H) 8.54 (dd, J=7.72, 1.84 Hz, 1 H) 8.88 (dd, J=4.78, 1.84 Hz, 1 H) 11.43 (s, 1 H) 14.02 (s, 1 H). MS (ESI) m/z 634 (M-H)⁻.

Example 424

methyl 2-chloro-6-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)isonicotinate

20 A mixture of the product of Example 321C (40.0 mg, 0.138 mmol), potassium carbonate (19.1 mg, 0.138 mmol), copper(II)oxide (18.4 mg, 0.23 mmol) and methyl 2,6-dichloroisonicotinate (28.4 mg, 0.138 mmol) in pyridine (0.2 mL) was stirred while heating at 125°C in a microwave reactor for 100 minutes. After cooling to 25°C, the mixture was loaded directly onto silica gel and eluted with a 0-5% methanol in dichloromethane step gradient. The fractions containing the desired product were combined and concentrated. The title compound was isolated by recrystallization of the residue using ethyl acetate/hexane (4.3 mg, 68%). MS (ESI) m/z 596 (M-H)⁻. ¹H NMR (300 MHz, CDCl₃) δ 1.13 (d, J=6.62 Hz, 6 H) 2.00 (m, 1 H) 2.84 (br m, 2 H) 3.99 (s, 3 H) 5.73 (br s, 1 H) 7.43 (m, 4 H) 7.62 (d, J=8.46 Hz, 1 H) 7.80 (m, 2 H) 7.96 (d, J=8.46 Hz, 1 H) 8.28 (d, J=8.09 Hz, 1 H) 14.37 (s, 1 H) 15.04 (s, 1 H).

Example 425A

35 4-(benzyloxy)-1-(3-methylbutyl)pyridin-2(1H)-one

A solution of 4-benzyloxy-1H-pyridin-2-one (1.0 g, 4.97 mmol) and 1-bromo-3-methyl butane (0.715 mL, 5.96 mmol) in N,N-dimethylformamide (20 mL) was treated with

1,8-diazabicyclo[5.4.0]undec-7-ene (1.86 mL, 12.43 mmol) at 65°C for 5 days. The mixture was cooled to 25°C and partitioned between water and dichloromethane. The organic layer was concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 1% methanol in dichloromethane to give the title compound (0.57 g, 42%). MS (DCI/NH₃) m/z 272 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃) δ 0.96 (d, J=6.25 Hz, 6 H) 1.61 (m, 3 H) 3.89 (m, 2 H) 4.99 (s, 2 H) 5.98 (dd, J=7.54, 2.76 Hz, 1 H) 6.06 (d, J=1.84 Hz, 1 H) 7.14 (d, J=7.72 Hz, 1 H) 7.39 (m, 5 H).

Example 425B

4-hydroxy-1-(3-methylbutyl)pyridin-2(1H)-one

A solution of the product of Example 425A (0.55 g, 2.03 mmol) in tetrahydrofuran (10 mL) was treated with ammonium formate (0.37 g, 5.87 mmol) and a catalytic amount of 20% palladium hydroxide on carbon at 60°C for 3 hours. The solution was filtered through diatomaceous earth and the filtrate was concentrated to yield the title compound (0.21 g, 57%). MS (DCI/NH₃) m/z 182 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃) δ 0.95 (d, J=6.25 Hz, 6 H) 1.60 (m, 3 H) 3.90 (m, 2 H) 6.09 (dd, J=7.35, 2.57 Hz, 1 H) 6.15 (d, J=2.21 Hz, 1 H) 7.17 (d, J=7.35 Hz, 1 H).

Example 425C

3-[bis(methylthio)methylene]-1-(3-methylbutyl)pyridine-2,4(1H,3H)-dione

A solution of the product of Example 425B (0.038 g, 0.21 mmol) in 1,4-dioxane (3 mL) was treated with pyridine (0.135 mL, 1.68 mmol) and tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi) (0.11 g, 0.42 mmol) at 40°C for 1 hour. Another portion of tris(methylthio)methyl methyl sulfate (0.11 g, 0.42 mmol) was added and the solution was heated at 85°C for 1 hour. The reaction mixture was cooled to 25°C and the solvent was removed under a stream of with warm nitrogen. The residue was chromatographed on a 1 gram Alltech sep-pack cartridge eluting with 100% dichloromethane followed by 30% ethyl acetate in dichloromethane to yield the title compound (19 mg, 33%). ¹H NMR (300 MHz, CHLOROFORM-D) δ 0.96 (d, J=6.25 Hz, 6 H) 1.58 (m, 3 H) 2.66 (s, 6 H) 3.78 (m, 2 H) 5.99 (d, J=7.35 Hz, 1 H) 7.06 (d, J=7.72 Hz, 1 H).

Example 425D

2-amino-5-[(methylsulfonyl)amino]benzenesulfonamide

A mixture of 2,5-diamino-benzenesulfonamide (0.288 g, 0.0015 mol, 1eq.), dichloromethane (5 mL), and pyridine (5 mL) was stirred at 0°C. Methanesulfonyl chloride (119 μL, 0.0015 mol, 1eq.) was added dropwise over 3 minutes. The reaction mixture was

warmed to 25° and stirred for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel using a step gradient of 0-4% methanol in dichloromethane to yield the title compound (68% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 2.87 (s, 3 H) 3.39 (s, 1 H) 5.80 (s, 1 H) 6.78 (d, J=8.82 Hz, 1 H) 7.13 (dd, J=8.64, 2.39 Hz, 1 H) 7.29 (s, 2 H) 7.45 (d, J=2.57 Hz, 1 H) 9.21 (m, 1 H). MS (ESI⁺) m/z=266 (M+H)⁺.

Example 425E

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydropyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

A solution of the product of Example 425C (0.019 g, 0.067 mmol) and the product of Example 425D (0.018 g, 0.067 mmol) in 1,4-dioxane was heated at 100°C for 1 hour. The solvent was removed under a stream of with warm nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous trifluoroacetic acid to yield the title compound (0.007 g, 23%). MS (ESI⁻) m/z 453 (M-H)⁻. ¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (d, J=6.25 Hz, 6 H) 1.58 (m, 3 H) 3.08 (s, 3 H) 3.99 (m, 2 H) 6.33 (d, J=6.62 Hz, 1 H) 7.57 (m, 2 H) 7.67 (d, J=8.82 Hz, 1 H) 8.07 (d, J=6.62 Hz, 1 H) 10.25 (s, 1 H) 13.84 (s, 1 H) 14.28 (s, 1 H).

Example 426A

1-benzyl-4-hydroxypyridin-2(1H)-one

The title compound was prepared by the method of Eschenhof, *et. al.*, Tetrahedron, v 48, 30, p 6225-6230, 1992.

Example 426B

1-benzyl-3-[bis(methylthio)methylene]pyridine-2,4(1H,3H)-dione

A solution of the product of Example 426A (0.124 g, 0.62 mmol) in 1,4-dioxane (6 mL) was treated with pyridine (0.400 mL, 4.96 mmol) and tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi) (0.32 g, 1.24 mmol) at 40°C for 15 minutes. Another portion of tris(methylthio)methyl methyl sulfate (0.32 g, 1.24 mmol) was added and the solution was heated at 90°C for 1 hour. The solvent was removed under a stream of with warm nitrogen and the residue was purified using a 1 gram Alltech sep-pack cartridge eluting with 100% dichloromethane followed by 30% ethyl acetate in dichloromethane to yield the title compound (79 mg, 42%). ¹H NMR (300 MHz, CHLOROFORM-D) δ 2.68 (s, 6 H) 4.99

(s, 2 H) 6.11 (d, $J=7.72$ Hz, 1 H) 7.17 (d, $J=8.09$ Hz, 1 H) 7.33 (m, 5 H).

Example 426C

N-[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide

A solution of the product of Example 426B (0.028 g, 0.092 mmol) and the product of Example 425D (0.025 g, 0.092 mmol) in 1,4-dioxane was heated at 100°C for 40 minutes. The solvent was removed under a stream of with warm nitrogen and the residue was triturated with water and ethyl acetate. The precipitate in the organic layer was filtered and dried to yield the title compound (0.006 g, 12%). MS (ESI) m/z 473 (M-H)⁻. ¹H NMR (500 MHz, DMSO-D₆) δ 3.06 (s, 3 H) 5.21 (s, 2 H) 6.38 (d, $J=4.88$ Hz, 1 H) 7.34 (m, 5 H) 7.55 (m, 3 H) 8.18 (d, $J=3.05$ Hz, 1 H) 10.25 (s, 1 H) 13.87 (s, 1 H) 14.05 (s, 1 H).

Example 427

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl)methyl]ethanesulfonamide

To a solution of the product of Example 353E (16.1 mg, 0.036 mmol) in N,N-dimethylformamide (0.4 mL) was added triethylamine (0.011 mL, 0.079 mmol). The mixture was cooled to 0°C and ethanesulfonyl chloride was added (0.0036 mL, 0.038 mmol). The mixture was warmed to 23°C and stirred for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10% acetonitrile in 0.1% trifluoroacetic acid in water to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (7.7 mg, 40 %). The sodium salt of the title compound was prepared by adding 1 N sodium hydroxide (0.029 mL, 0.0029 mmol) to a solution of the title compound (7.7 mg, 0.014 mmol) in water (0.4 mL) and stirring for thirty minutes. The reaction mixture was concentrated under reduced pressure. ¹H NMR (300 MHz, DMSO-d₆) δ 0.21 (bs, 2 H) 0.46 (d, 2 H) 0.99 (m, 1 H) 1.19 (t, 3 H) 3.01 (q, 2 H) 4.23 (s, 2 H) 5.85 (t, $J=6.62$ Hz, 1 H) 6.79 (s, 1 H) 6.93 (t, $J=7.54$ Hz, 1 H) 7.35 (t, $J=6.99$ Hz, 2 H) 7.59 (d, $J=8.09$ Hz, 1 H) 7.95 (d, $J=6.62$ Hz, 1 H).

Example 428

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl)methyl]propane-1-sulfonamide

To a solution of the product of Example 353E (16.7 mg, 0.037 mmol) in N,N-dimethylformamide (0.4 mL) was added triethylamine (0.011 mL, 0.079 mmol). The mixture was cooled to 0°C and 1-propane sulfonyl chloride was added (0.005 mL, 0.041

mmol). The mixture was warmed to 23°C and stirred for 1.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10% acetonitrile/0.1% trifluoroacetic acid in water to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (9.9 mg, 48%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.15 (d, *J*=4.04 Hz, 2 H) 0.42 (d, *J*=7.35 Hz, 2 H) 0.99 (m, 4 H) 1.69 (m, 2 H) 2.84 (d, *J*=7.35 Hz, 2 H) 3.06 (m, 2 H) 4.27 (d, *J*=6.25 Hz, 2 H) 6.35 (bs, 1 H) 7.37 (s, 1 H) 7.42 (t, *J*=7.54 Hz, 2 H) 7.75 (t, *J*=6.07 Hz, 1 H) 7.87 (t, *J*=7.17 Hz, 1 H) 8.07 (d, *J*=8.46 Hz, 1 H) 8.15 (dd, 1 H) 14.52 (bs, 1 H).

Example 429N-[3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]propane-2-sulfonamide

To a solution of the product of Example 353E (16.2 mg, 0.036 mmol) in *N,N*-dimethylformamide (0.4 mL) was added triethylamine (0.011 mL, 0.079 mmol). The mixture was cooled to 0°C and isopropyl sulfonyl chloride was added (0.0043 mL, 0.038 mmol). The mixture was warmed to 23°C and stirred for 3 hours. Additional isopropyl sulfonyl chloride (0.006 mL, 0.055 mmol) was added and the reaction mixture was stirred at 23°C for 15 hours. The reaction mixture was stirred at 50°C for 2 hours. Additional triethylamine (0.040 mL, 0.287 mmol) and isopropyl sulfonyl chloride (0.010 mL, 0.091 mmol) were added and the reaction mixture was stirred at 50°C for 2 hours. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10% acetonitrile/0.1% trifluoroacetic acid in water to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (6.7 mg, 33%). The sodium salt of the title compound was prepared according to the procedure of Example 1D. ¹H NMR (300 MHz, DMSO-d₆) δ 0.21 (bs, 2 H) 0.48 (d, 2 H) 0.98 (m, 1 H) 1.24 (d, *J*=6.99 Hz, 6 H) 3.19 (m, 1 H) 4.25 (s, 2 H) 5.85 (t, 1 H) 6.76 (s, 1 H) 6.92 (t, 1 H) 7.34 (m, 2 H) 7.57 (d, 1 H) 7.96 (d, 1 H).

Example 430

N-[3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]benzenesulfonamide

To a solution of the product of Example 353E (16.9 mg, 0.038 mmol) in *N,N*-dimethylformamide (0.4 mL) was added triethylamine (0.012 mL, 0.083 mmol) and benzene sulfonyl chloride (0.006 mL, 0.042 mmol). The reaction mixture was stirred at 23°C for 0.75 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10% acetonitrile/0.1% trifluoroacetic acid in water to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (10.7 mg, 48%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.14 (d, *J*=4.04 Hz, 2 H)

0.41 (d, $J=7.72$ Hz, 2 H) 1.01 (m, $J=7.54$, 7.54 Hz, 1 H) 2.83 (d, $J=6.99$ Hz, 2 H) 4.07 (d, $J=6.25$ Hz, 2 H) 6.38 (bs, 1 H) 7.30 (s, 1 H) 7.41 (t, $J=7.54$ Hz, 1 H) 7.65 (m, 3 H) 7.86 (m, 3 H) 8.06 (d, $J=8.82$ Hz, 1 H) 8.15 (d, $J=6.99$ Hz, 1 H) 8.42 (t, $J=6.25$ Hz, 1 H) 14.43 (bs, 1 H).

5

Example 431

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]-1-phenylmethanesulfonamide

To a solution of the product of Example 353E (16.5 mg, 0.037 mmol) in *N,N*-dimethylformamide (0.4 mL) was added triethylamine (0.011 mL, 0.079 mmol). The mixture was cooled to 0°C and α -toluene sulfonyl chloride was added (0.008 g, 0.041 mmol). The reaction mixture was warmed to 23°C and stirred for 0.5 hours. The reaction mixture was then heated to 50°C and stirred for 1.75 hours. Additional triethylamine (0.010 mL, 0.074 mmol) and α -toluene sulfonyl chloride (0.007 g, 0.037 mmol) were added and the reaction mixture was stirred at 23°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase chromatography, eluting with a gradient of 10% acetonitrile/0.1% trifluoroacetic acid in water to 95% acetonitrile/0.1% trifluoroacetic acid in water to give the title compound (7.7 mg, 35%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.15 (d, $J=4.04$ Hz, 2 H) 0.42 (d, $J=7.72$ Hz, 2 H) 1.00 (m, 1 H) 2.84 (d, $J=7.35$ Hz, 2 H) 4.23 (d, $J=5.52$ Hz, 2 H) 4.44 (s, 2 H) 6.37 (bs, 1 H) 7.32 (s, 1 H) 7.42 (m, 6 H) 7.86 (m, 2 H) 8.07 (d, $J=8.46$ Hz, 1 H) 8.16 (dd, 1 H) 14.50 (bs, 1 H).

25

Example 432A

1-(cyclobutylamino)-4-hydroxyquinolin-2(1*H*)-one

A solution of the product of Example 350A (0.516 g, 2.9 mmol) and cyclobutanone (1.05 g, 15.0 mmol) in acetic acid (0.90 g, 15.0 mmol) and methanol (20 mL) was treated portion wise with sodium cyanoborohydride (0.94 g, 15.0 mmol), stirred for 48 hours and concentrated. The residue was treated with 0.5 M aqueous sodium bicarbonate, acidified to pH 2 with 1M hydrochloric acid and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude material was chromatographed on silica gel eluting with 3:2 hexane/ethyl acetate to give the title compound (0.400 g, 60 %). MS (ESI⁺) m/z 231 (M+H)⁺. ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.52 (m, 1 H) 1.63 (m, 1 H) 1.96 (m, 4 H) 3.64 (m, 1 H) 5.91 (s, 1 H) 6.26 (d, $J=6.62$ Hz, 1 H) 7.20 (t, $J=8.09$ Hz, 1 H) 7.61 (m, 1 H) 7.84 (m, 2 H) 11.42 (s, 1 H).

Example 432B3-[bis(methylthio)methylene]-1-(cyclobutylamino)quinoline-2,4(1H,3H)-dione

A solution of the product of Example 432A (0.115 g, 0.5 mmol) and tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi) (0.27 g, 1.0 mmol) in pyridine (0.316 g, 4.0 mmol) and dioxane (5.0 mL) was heated at 60°C for 30 minutes. Additional tris(methylthio)methyl methyl sulfate was added (0.27 g, 1.0 mmol) and heating continued for 30 minutes. The mixture was cooled to 25°C and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, brine, dried over sodium sulfate, filtered and concentrated. The crude material was chromatographed on silica gel eluting with 95/5 dichloromethane/ethyl acetate to give the title compound (0.146 g, 87 % yield). MS (ESI⁺) m/z 335 (M+H)⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 1.54 (m, 1 H) 1.66 (m, 1 H) 1.99 (m, 4 H) 2.61 (s, 6 H) 3.62 (m, 1 H) 6.18 (d, J=6.25 Hz, 1 H) 7.15 (t, J=7.54 Hz, 1 H) 7.63 (m, 1 H) 7.72 (d, J=8.09 Hz, 1 H) 7.98 (dd, J=7.91, 1.29 Hz, 1 H).

Example 432CN-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

A mixture of the product of Example 425D (0.195 g, 0.585 mmol, 1.5 eq.) and the product of Example 432B (0.100g, 0.390mmol, 1.5 eq.) in anhydrous dioxane (10 mL) was heated for 1 hour at 120°C. After cooling to 25°C, the reaction mixture was treated with methanol (20 mL) and diethyl ether (20 mL) and the precipitated product collected by vacuum filtration to yield the title compound (25 mg, 12% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 1.69 (m, 2 H) 2.13 (m, 4 H) 3.10 (s, 3 H) 3.77 (m, 1 H) 6.57 (s, 1 H) 7.44 (t, J=7.35 Hz, 1 H) 7.65 (m, 3 H) 7.89 (t, J=7.35 Hz, 1 H) 8.06 (d, J=8.46 Hz, 1 H) 8.16 (d, J=7.72 Hz, 1 H) 10.31 (s, 1 H) 14.16 (s, 1 H) 15.03 (s, 1 H). MS (ESI⁺) m/z=504 (M+H)⁺.

Example 433N-(3-{1-[1-(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide

A solution of the product of Example 353B (0.090 g, 0.269 mmol, 1 eq.), and the product of Example 425D (0.071g, 0.269mmol, 1 eq.), in anhydrous dioxane (5 mL) was heated for 1 hour at 120°C. After cooling the reaction mixture to 25°C, methanol (20 mL) and diethyl ether (20 mL) were added and the precipitated product collected by vacuum filtration to give the title compound (21 mg, 15.5% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 0.16 (m, 2 H) 0.41 (m, 2 H) 1.07 (m, 1 H) 2.85 (m, 2 H) 3.10 (s, 3 H) 6.44 (m, 1 H) 7.44 (t, J=7.54 Hz, 1 H) 7.62 (m, 2 H) 7.71 (m, 1 H) 7.90 (t, J=7.91 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1

H) 8.17 (d, $J=6.99$ Hz, 1 H) 10.30 (m, 1 H) 14.15 (m, 1 H). MS (ESI⁺) $m/z=504$ (M+H)⁺.

Example 434

4-hydroxy-3-[8-(hydroxymethyl)-1,1-dioxido-4,9-dihydroimidazo[4,5-
h][1,2,4]benzothiadiazin-3-yl]-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one

The product of Example 377 (14 mg, 0.033 mmole) was treated with 4N HCl (0.5 mL) and glycolic acid (4 mg, 0.052 mmole) and the resulting mixture was heated 24 hours at reflux. The mixture was concentrated under reduced pressure to a white pasty solid. The solid was purified by chromatography on silica gel eluting with 95:5
dichloromethane:methanol to give the title compound (10 mg, 63%). The title compound was converted to the sodium salt as described in Example 1D. MS (ESI⁺) m/z : 483. ¹H NMR (300 MHz, DMSO- d_6) δ 0.97 (d, $J=6.25$ Hz, 6 H) 1.50 (s, 1 H) 1.64 (d, $J=6.99$ Hz, 1 H) 3.87 (s, 1 H) 4.08 (d, $J=6.62$ Hz, 1 H) 4.30 (d, $J=6.99$ Hz, 1 H) 4.54 (s, 1 H) 4.66 (d, $J=6.62$ Hz, 1 H) 4.73 (s, 1 H) 5.33 (d, $J=6.62$ Hz, 1 H) 7.04 (d, $J=8.82$ Hz, 1 H) 7.14 (dd, $J=7.35, 4.78$ Hz, 1 H) 7.76 (d, $J=8.82$ Hz, 1 H) 8.39 (dd, $J=7.54, 2.02$ Hz, 1 H) 8.53 (m, 1 H) 12.49 (s, 1 H).

Example 435A

2-chloroethyl ({3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-
1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}amino)sulfonylcarbamate

A solution of chlorosulfonyl isocyanate (33 mg, 0.23 mmol) in dichloromethane (8 mL) was cooled to 0°C and 2-chloroethanol (18.8 mg, 0.23 mmol) was added dropwise. The mixture was stirred at 0°C for 90 minutes followed by the addition of a solution containing the product of Example 205 (100 mg, 0.23 mmol) and triethylamine (71 mg, 0.70 mmol) in dichloromethane (2 mL). The mixture was stirred for 24 hrs at 25°C then partitioned between dichloromethane (25 mL) and 1N aqueous hydrochloric acid (20 mL). The resulting organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (96 mg, 67%). MS (ESI⁺) m/z 611 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d_6) δ 0.98 (d, $J=6.62$ Hz, 6 H) 1.57 (m, 2 H) 1.69 (m, 1 H) 3.78 (m, 2 H) 4.32 (m, 2 H) 4.49 (m, 2 H) 7.51 (m, 2 H) 7.63 (s, 1 H) 7.77 (d, $J=9.19$ Hz, 1 H) 8.56 (dd, $J=7.72, 1.10$ Hz, 1 H) 8.90 (dd, $J=4.41, 1.47$ Hz, 1 H) 11.15 (s, 1 H) 12.26 (s, 1 H) 14.10 (s, 1 H).

Example 435B

N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-dioxido-

4H-1,2,4-benzothiadiazin-7-yl}-2-oxo-1,3-oxazolidine-3-sulfonamide To a solution of the product of Example 435A (90 mg, 0.147 mmol) in dichloromethane (10 mL) was added triethylamine (1 mL). The mixture was stirred at 25°C for 6 hours. The reaction was treated with 1N aqueous hydrochloric acid (10 mL) and extracted with dichloromethane (20 mL).

5 The organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound as a colorless solid (70 mg, 82%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.69 (m, 1 H) 3.98 (m, 2 H) 4.36 (m, 2 H) 4.48 (m, 2 H) 7.49 (dd, J=7.72, 4.78 Hz, 1 H) 7.60 (m, 1 H) 7.62 (s, 1 H) 7.75 (d, J=8.82 Hz, 1 H) 8.56 (m, 1 H) 8.89 (m, 1 H) 11.59 (s, 1 H) 14.15 (s, 1 H).

Example 435C

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-N'-(2-phenylethyl)sulfamide

A mixture of the product of Example 435B (28 mg, 0.05mmole) and phenethylamine (6 mg, 0.05 mmol) in acetonitrile (10 mL) and triethylamine (0.5 mL) was heated at reflux for 18 hours. The reaction mixture was cooled to 25°C, diluted with ethyl acetate, extracted with 10 mL 1 N HCl, followed by 10 mL brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The product was isolated by preparative thin layer chromatography on silica gel eluting with 25 % ethyl acetate in dichloromethane to provide 2 mg of the title compound (10% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.57 (m, 2 H) 1.69 (m, 1 H) 2.68 (m, 2 H) 3.09 (m, 2 H) 4.49 (m, 2 H) 7.20 (m, 5 H) 7.46 (m, 1 H) 7.51 (m, 1 H) 7.60 (d, J=2.21 Hz, 1 H) 7.68 (d, J=8.82 Hz, 1 H) 7.97 (m, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (m, 1 H) 10.28 (s, 1 H) 14.13 (s, 1 H) 15.23 (s, 1 H).

Example 436

benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide

A solution of chlorosulfonyl isocyanate (24.5 μL, 0.281 mmol) in dichloromethane (2 mL) was treated dropwise with benzyl alcohol (29 μL, 0.281 mmol) at 25°C, stirred at 25°C for 30 min, treated with a solution of the product of Example 205 (100 mg, 0.234 mmol) and triethylamine (130 μL, 0.936 mmol) in dichloromethane (3 mL) and stirred for 2 hrs at 25°C. The reaction mixture was treated with dichloromethane (10 mL) and 1N aqueous hydrochloric acid (10 mL). The resulting organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (122 mg, 81%). MS (ESI) m/z 639 (M-H). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J = 6.6 Hz, 6H), 1.59 (m, 2H), 1.66 (m, 1H), 4.49 (m, 2H), 5.12 (s, 2H), 7.32 (m,

5H), 7.48 (m, 2H), 7.65 (d, $J = 2.2$ Hz, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 8.57 (dd, $J = 7.7, 1.8$ Hz, 1H), 8.90 (dd, $J = .8, 1.8$ Hz, 1H), 11.17 (s, 1H), 12.19 (bs, 1H), 14.11 (bs, 1H).

Example 437

5 *N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]sulfamide

A solution of the product of Example 436 (40 mg, 0.0625 mmol) in methanol (5 mL) was treated with 10% palladium on carbon (20 mg), and stirred at 25°C for 5 hours under hydrogen atmosphere. The resulting solution was then filtered and the filtrate concentrated under reduced pressure to provide the title compound (25 mg, 78%). MS (ESI) m/z 505 (M-H)⁻. ¹H NMR (300 MHz, DMSO- d_6) δ ppm 0.98 (d, $J = 6.3$ Hz, 6H), 1.57 (m, 2H), 1.66 (m, 1H), 4.42 (m, 2H), 7.38 (m, 1H), 7.43 (m, 2H), 7.59 (m, 1H), 8.52 (m, 1H), 8.82 (bs, 1H), 9.99 (bs, 1H).

Example 438

15 benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]-1-propyldiazathiane-1-carboxylate 2,2-dioxide

A solution of triphenylphosphine (1.5 eq) in dichloromethane is treated dropwise with diethyl azodicarboxylate (1.5 eq) at 25°C. The solution is allowed to stir for 10 min followed by the dropwise addition of a solution containing the product of Example 436 (1 eq) and *n*-propanol (1.1 eq) in dichloromethane. The resulting solution is stirred at 25°C for 20 hours, followed by the addition of dichloromethane and 1N aqueous hydrochloric acid. The resulting organic layer is separated and dried over magnesium sulfate, and filtered to provide the title compound.

Example 439

25 *N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]-*N'*-propylsulfamide

A solution of the product of Example 438 in methanol is treated with 10% palladium on carbon and stirred at 25°C for 5 hours under hydrogen atmosphere. The resulting solution is then filtered and the filtrate concentrated under reduced pressure to provide the title compound.

35 Example 440 methyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide

To a stirred solution of chlorosulfonyl isocyanate (4.9 μ L, 0.0562 mmol) in dichloromethane (2 mL) was added dropwise methanol (2.3 μ L, 0.0562 mmol) at 25°C. After

30 minutes, a solution of the product of Example 205 (20 mg, 0.0468 mmol) and triethylamine (26 μ L, 0.187 mmol) in dichloromethane (2 mL) was added and stirred for 24 hours at 25°C. The reaction mixture was diluted with dichloromethane (10 mL) and 1N aqueous hydrochloric acid (10 mL). The resulting organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (12 mg, 39%) as a triethylamine salt. ^1H NMR (300 MHz, DMSO- d_6) δ 0.98 (d, J = 6.3 Hz, 3H), 1.38 (m, 2H), 1.67 (m, 1H), 3.63 (s, 3H), 4.50 (m, 2H), 7.53 (m, 2H), 7.63 (d, J = 2.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 8.57 (dd, J = 8.1, 1.8 Hz, 1H), 8.90 (dd, J = 4.4, 1.8 Hz, 1H), 11.15 (s, 1H), 12.10 (s, 1H), 14.10 (s, 1H). MS (ESI) m/z 563 (M-H) $^-$.

10 Example 441 benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-methyldiazathiane-1-carboxylate 2,2-dioxide

A solution of the product of Example 436 (0.032 g, 0.05 mmol) in 1:1 tetrahydrofuran / methanol (2 ml) at -10°C was treated dropwise with trimethylsilyl diazomethane (2.0 M in hexanes, 50 μ L, 0.1 mmol), then stirred at 25°C for 16 hours and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 3% methanol in dichloromethane to provide the title compound (5 mg, 15% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 0.99 (d, J =6.25 Hz, 6 H) 1.58 (m, 2 H) 1.69 (m, 1 H) 3.21 (s, 3 H) 4.49 (m, 2 H) 5.19 (s, 2 H) 7.32 (m, 5 H) 7.46 (m, 1 H) 7.51 (dd, J =7.91, 4.60 Hz, 1 H) 7.58 (d, J =2.21 Hz, 1 H) 7.68 (d, J =8.82 Hz, 1 H) 8.57 (dd, J =8.09, 1.84 Hz, 1 H) 8.90 (dd, J =4.78, 1.47 Hz, 1 H) 11.29 (s, 1 H) 14.09 (s, 1 H). MS (ESI) m/z 653 (M-H) $^-$.

Example 442 N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-N'-methylsulfamide

A solution of the product of Example 441 (14 mg, 0.0214 mmol) in methanol (3 mL) was reacted with 10% palladium on carbon (10 mg) under a hydrogen atmosphere at 25°C with stirring for 2 hours. The solution was filtered and concentrated under reduced pressure to provide the title compound (8 mg, 73%). ^1H NMR (300 MHz, DMSO- d_6) δ 0.94 (d, J = 6.6 Hz, 6H), 1.57 (m, 2H), 1.69 (m, 1H), 2.49 (s, 3H), 4.45 (m, 2H), 7.50 (m, 2H), 7.62 (m, 2H), 8.57 (m, 1H), 8.84 (m, 1H), 10.18 (bs, 1H). MS (ESI) m/z 519 (M-H) $^-$.

Example 443

2-aminoethyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide

To a solution of chlorosulfonyl isocyanate (7.3 μ L, 0.0843 mmol) in dichloromethane (2 mL) was added *t*-butyl N-(2-hydroxyethyl)carbamate (13.6 mg, 0.0843 mmol) at 25°C. After 30 minutes, the solution was treated with a solution of the product of Example 205 (30 mg, 0.0703 mmol) and triethylamine (39 μ L, 0.281 mmol) in dichloromethane (2 mL) and

stirred for 24 hours. The reaction mixture was diluted with dichloromethane (10 mL) and 1N aqueous hydrochloric acid (10 mL). The resulting organic layer was separated and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min to provide 8 mg of a solid. This solid was treated with a solution of trifluoroacetic acid (1.6 mL) and dichloromethane (0.4 mL) at 25°C for 3 hours. The solvent was removed under reduced pressure to provide the title compound (12 mg, 24%) as a trifluoroacetic acid salt. ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, *J* = 6.6 Hz, 6H), 1.57 (m, 2H), 1.68 (m, 1H), 3.06 (m, 2H), 4.21 (t, *J* = 5.1 Hz, 2H), 4.46 (m, 2H), 7.49 (m, 2H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.83 (bs, 2H), 8.55 (dd, *J* = 7.7, 1.8 Hz, 1H), 8.86 (m, 1H). MS (ESI) *m/z* 592 (M-H)⁻.

Example 444

N-cyclopentyl-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]sulfamide

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added 1-amino cyclopentane (0.0085 g, 0.0099 mL, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen gas, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (11 mg, 38%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.97 (d, *J*=6.62 Hz, 6 H) 1.51 (m, 11 H) 3.53 (m, 1 H) 4.48 (m, 2 H) 7.49 (m, 2 H) 7.60 (d, *J*=2.57 Hz, 1 H) 7.70 (d, *J*=9.19 Hz, 1 H) 7.83 (d, *J*=7.35 Hz, 1 H) 8.55 (dd, *J*=8.09, 1.84 Hz, 1 H) 8.88 (dd, *J*=4.60, 1.65 Hz, 1 H) 10.19 (s, 1 H) 14.06 (s, 1 H). (ESI-) *m/z* 573 (M-H)⁻.

Example 445

N-cyclobutyl-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]sulfamide

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added 1-amino cyclobutane (0.0071 g, 0.0085 mL, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen gas, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size)

using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (8 mg, 28%). ¹H NMR (300 MHz, DMSO- d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.64 (m, 7 H) 2.05 (m, 2 H) 3.68 (m, 1 H) 4.49 (m, 2 H) 7.50 (m, 2 H) 7.59 (d, J=2.57 Hz, 1 H) 7.73 (d, J=8.82 Hz, 1 H) 8.16 (d, J=8.46 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.60, 1.65 Hz, 1 H) 10.17 (s, 1 H) 14.02 (s, 1 H). MS (ESI-) m/z 559 (M-H)⁺.

A-825309.1

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Example 446A

tert-butyl 4-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino]sulfonylamino]-1-piperidinecarboxylate

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To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added N-1-Boc-4-amino piperidine (0.020 g, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen gas, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (12 mg, 35%).

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Example 446B

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-N'-(4-piperidiny)lsulfamide

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The product of Example 446A (0.012 g, 0.017 mmol) was dissolved in the solution of hydrogen chloride in 1,4-dioxane (4 N, 3 mL). The mixture was stirred at 25°C for 18 hours. The solvent was removed under reduced pressure to give the title compound as its hydrochloride salt (10 mg, 92%). ¹H NMR (300 MHz, DMSO- d₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.70 (m, 7 H) 2.95 (m, 2 H) 3.16 (m, 3 H) 4.49 (m, 2 H) 7.50 (m, 2 H) 7.63 (d, J=2.21 Hz, 1 H) 7.73 (d, J=9.19 Hz, 1 H) 8.17 (d, J=7.35 Hz, 1 H) 8.52 (m, 1 H) 8.56 (dd, J=7.91, 1.65 Hz, 1 H) 8.75 (m, 1 H) 8.90 (dd, J=4.60, 1.65 Hz, 1 H) 10.34 (s, 1 H) 14.08 (s, 1 H). MS (ESI-) m/z 588 (M-H)⁺.

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A-825311.0 Example 447 DL2

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N-(2-hydroxyethyl)-N'-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide

To the product of Example 435 B (0.006 g, 0.0104 mmol) in tetrahydrofuran (2 ml)

was added water (0.1 ml) and sodium ethoxide in ethanol (20% w/w, 1 ml). The mixture was stirred for 24 hours at 25°C. The reaction was concentrated under a stream of warm nitrogen gas, and the residue was treated with 1N hydrochloric acid (2 ml) with stirring for 10 min.

The resulting solid was filtered and dried to give the title compound (4 mg, 70%). ¹H NMR (300 MHz, DMSO- d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.71 (m, 1 H) 2.92 (m, 2 H) 3.39 (m, 2 H) 4.50 (m, 2 H) 7.51 (m, 2 H) 7.61 (d, J=2.21 Hz, 1 H) 7.72 (d, J=8.82 Hz, 1 H) 7.80 (t, J=5.88 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.89 (dd, J=4.41, 1.47, 1 H) 10.21 (s, 1 H) 14.08 (s, 1 H). MS (ESI-) m/z 549 (M-H)⁻.

Example 4483-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]propanamide

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added glycineamide hydrochloride (0.0125 g, 0.1 mmol) and potassium carbonate (0.4 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen gas and, the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (3 mg, 10%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.59 (m, 2 H) 1.70 (m, 1 H) 2.25 (t, J=7.54 Hz, 2 H) 3.07 (m, 2 H) 4.49 (m, 2 H) 6.80 (s, 1 H) 7.30 (s, 1 H) 7.50 (m, 2 H) 7.61 (d, J=2.21 Hz, 1 H) 7.70 (d, J=8.82 Hz, 1 H) 7.82 (t, J=5.70 Hz, 1 H) 8.56 (dd, J=7.72, 1.84 Hz, 1 H) 8.89 (dd, J=4.41 Hz, 1.47 Hz, 1 H) 10.23 (s, 1 H) 14.13 (s, 1 H). MS (ESI-) m/z 576 (M-H)⁻.

A-832731.0 Example 449

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-azetidinesulfonamide

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added azetidine hydrochloride (0.0095 g, 0.1 mmol) and potassium carbonate (0.4 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (2 mg, 7%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.71 (m, 1 H) 2.15 (m, 2 H) 3.83 (t, J=7.54 Hz, 4 H) 4.49 (m, 2 H) 7.53 (m, 2 H) 7.63 (d, J=2.21 Hz, 1 H) 7.72 (d, J=9.19 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H) 10.50 (s, 1 H) 14.11 (s, 1 H). MS (ESI-) m/z 545 (M-H)⁻.

A-832735.0 Example 450 DL23-hydroxy-N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-azetidinesulfonamide

5 To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added 3-hydroxyazetidine hydrochloride (0.011 g, 0.1 mmol) and potassium carbonate (0.4 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column
 10 (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (3 mg, 13%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.58 (m, 2 H) 1.71 (m, 1 H) 3.66 (m, 2 H) 3.92 (m, 2 H) 4.38 (m, 1 H) 4.50 (m, 2 H) 7.55 (m, 3 H) 7.73 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=8.09 Hz, 1.08 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H) 10.55 (s, 1 H) 14.08 (s, 1 H). MS (ESI-) m/z 561 (M-H)⁻.

Example 451Atert-butyl 1-({[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]amino}sulfonyl)-3-pyrrolidinylcarbamate

20 To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added N-Boc-3-amino pyrrolidine (0.0186 g, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative
 25 HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (23 mg, 68%).

Example 451B3-amino-N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-pyrrolidinesulfonamide

30 The product of Example 446A (0.012 g, 0.017 mmol) was dissolved in a solution of hydrogen chloride in 1,4-dioxane (4N, 3 mL). The mixture was stirred at 25°C for about 18 hours. The solvent was removed under reduced pressure to give the title compound as its
 35 hydrochloride salt (16 mg, 88%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.54 (m, 2 H) 1.67 (m, 1 H) 1.91 (m, 1 H) 2.18 (m, 1 H) 3.26 (m, 2 H) 3.50 (m, 2 H) 3.79 (m, 1 H) 4.43 (m, 2 H) 7.40 (dd, J=7.72, 4.78 Hz, 1 H) 7.58 (m, 3 H) 8.22 (s, 3 H) 8.50 (dd,

J=7.71 Hz, 1.47 Hz, 1 H) 8.80 (d, J=3.31 Hz, 1 H) 10.52 (s, 1 H) 14.55 (s, 1 H). MS (ESI-) m/z 574 (M-H)⁻.

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Example 452A1-piperidinesulfonyl chloride

A solution of sulfuryl chloride (1N in dichloromethane, 75 mL, 75 mmol) at -20°C was treated dropwise with piperidine (12.6 g, 150 mmol), stirred at 0°C for 2 hours, and partitioned between dichloromethane and water (50 mL). The organic layer was washed with aqueous 1N HCl, brine and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure (1 mm Hg) at 105°C to give the title compound (5 grams).

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Example 452BN-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-piperidinesulfonamide

A mixture of the product of Example 205 (2 mg, 0.1 ml), the product of Example 451A (17 mg, 0.1 mmol) and triethylamine (0.1 mL) in dichloromethane (2 mL) was stirred for 18 hours at 25°C, diluted with dichloromethane (25 mL) and washed with 1 N HCl and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min to provide the title compound (10 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.62 Hz, 6 H) 1.43 (s, 6 H) 1.57 (m, 2 H) 1.69 (m, 1 H) 3.14 (s, 4 H) 4.49 (m, 2 H) 7.51 (m, 1 H) 7.53 (s, 1 H) 7.60 (d, J=2.21 Hz, 1 H) 7.72 (d, J=8.82 Hz, 1 H) 8.56 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.78, 1.84 Hz, 1 H) 10.47 (s, 1 H) 14.06 (s, 1 H) 15.05 (s, 1 H). MS (ESI-) m/z 573 (M-H)⁻.

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A-805330.0 Example 453 DLMN-benzyl-N'-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide

A mixture of the product of Example 435B (28 mg, 0.05mmole), benzylamine (6 mg, 0.05 mmol) and triethylamine (0.5 mL) in acetonitrile (2 mL) was stirred at 70°C for 18 hours. The reaction mixture was cooled to about 25°C, partitioned between ethyl acetate and 1 N HCl (10 mL). The organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by

reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min to give the title compound (12 mg). ¹H NMR (300 MHz, DMSO- d₆) δ 0.99 (d, *J*=6.25 Hz, 6 H) 1.65 (m, 3 H) 4.08 (d, *J*=6.25 Hz, 2 H) 4.49 (m, 2 H) 7.22 (m, 5 H) 7.45 (m, 1 H) 7.51 (dd, *J*=8.09, 4.78 Hz, 1 H) 7.61 (d, *J*=2.57 Hz, 1 H) 7.69 (d, *J*=8.82 Hz, 1 H) 8.41 (t, *J*=6.25 Hz, 1 H) 8.57 (dd, *J*=8.09, 1.84 Hz, 1 H) 8.90 (dd, *J*=4.78, 1.84 Hz, 1 H) 10.33 (s, 1 H) 14.08 (s, 1 H) 15.15 (s, 1 H). MS (ESI⁺) *m/z* 595 (M-H)⁻.

10 Example 454 ethyl 3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]benzoate

A solution of 3-amino-benzoic acid ethyl ester (0.165 g, 1.0 mmol) in dichloromethane (6 mL) at about 0°C was added dropwise with chlorosulfonic acid (0.128 g, 1.1 mmol). The reaction mixture was stirred at 25°C for 1 h and then phosphorous pentachloride (0.229 g, 1.1 mmol) was added and the reaction mixture heated under reflux for 3.5 hours. The reaction mixture was then cooled to about 25°C and the solvent evaporated under reduced pressure. A solution of the residue in dichloromethane (10 mL) was treated with the product of Example 205 (0.214 g, 0.5 mmol), followed by triethylamine (0.152 g, 1.5 mmol). The reaction mixture was stirred at 25°C for 3 hours and then poured into 25mL of 1N aqueous hydrochloric acid. The reaction mixture was then extracted with dichloromethane (3 x 25 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with 0-2% methanol/dichloromethane to provide the title compound (0.166 g, 48% yield). ¹H NMR (300 MHz, DMSO- d₆) δ 0.98 (d, *J*=6.25 Hz, 6 H) 1.30 (t, *J*=7.17 Hz, 3 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 4.29 (q, *J*=6.99 Hz, 2 H) 4.48 (m, 2 H) 7.44 (m, 4 H) 7.57 (d, *J*=2.21 Hz, 1 H) 7.62 (dt, *J*=7.36, 1.47 Hz, 1 H) 7.69 (d, *J*=8.82 Hz, 1 H) 7.74 (s, 1 H) 8.55 (dd, *J*=8.09, 1.84 Hz, 1 H) 8.88 (dd, *J*=4.41, 1.84 Hz, 1 H) 10.80 (s, 1 H) 10.88 (s, 1 H) 14.11 (s, 1 H). MS (ESI⁺) *m/z* 655.1 (M+H)⁺, 672.2 (M+NH₄)⁺, 677.0 (M+Na)⁺, (ESI⁻) *m/z* 653.1 (M-H)⁻.

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A-824028.0 Example 455

3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]benzoic acid

A solution of the product of Example 454 (25.5 mg, 0.389 mmol) in 1 mL of 1N aqueous sodium hydroxide and 1 mL of methanol was stirred at 25°C for 17 hours, and concentrated under a stream of warm nitrogen. The residue was treated with 2 mL of 1N aqueous hydrochloric acid. The resulting solid was isolated by vacuum filtration, washed

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with 10 mL of water, and dried to provide the title compound (21.4 mg, 88% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, *J*=6.62 Hz, 6 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 4.48 (m, 2 H) 7.32–7.53 (m, 4 H) 7.59 (m, 2 H) 7.69 (d, *J*=8.82 Hz, 1 H) 7.75 (s, 1 H) 8.55 (dd, *J*=8.09, 1.84 Hz, 1 H) 8.88 (dd, *J*=4.78, 1.47 Hz, 1 H) 10.79 (s, 1 H) 10.88 (s, 1 H) 13.01 (bs, 1 H) 14.12 (bs, 1 H). MS (ESI⁺) *m/z* 627.1 (M+H)⁺, 649.1 (M+Na)⁺, (ESI⁻) *m/z* 625.1 (M-H)⁻.

Example 4563-[(1-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]amino)sulfonyl)amino]benzamide

A solution of the product of Example 454 (7.6 mg, 0.012 mmol) in 1 mL of ammonium hydroxide was stirred at 25°C for 17 hours. The solvent was evaporated under a stream of warm nitrogen to provide the title compound (7.4 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 0.96 (d, *J*=6.62 Hz, 6 H) 1.47 (m, 2 H) 1.64 (m, 1 H) 4.30 (m, 2 H) 7.14 (m, 1 H) 7.28 (m, 6 H) 7.43 (s, 1 H) 7.49 (d, *J*=7.72 Hz, 1 H) 7.66 (s, 1 H) 7.87 (s, 1 H) 8.36 (dd, *J*=7.54, 1.65 Hz, 1 H) 8.54 (s, 1 H) 10.45 (bs, 1 H) 10.51 (bs, 1 H) 15.89 (bs, 1 H).

Example 457A4-(benzyloxy)-1-isopentyl-2(1*H*)-pyridinone

A solution of 4-benzyloxy-1*H*-pyridin-2-one (1.0 g, 4.97 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.86 mL, 12.43 mmol) and 1-bromo-3-methyl butane (0.715 mL, 5.96 mmol) in *N,N*-dimethylacetamide (20 mL) was heated at 65°C for 5 days. The solution was cooled to about 25°C and partitioned between 10% aqueous ammonium chloride and dichloromethane, the organic layer separated and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with 1% methanol in dichloromethane to provide the title compound (0.569 g, 42%).

Example 457B

4-hydroxy-1-isopentyl-2(1*H*)-pyridinone

The product of Example 457A (0.452 g, 1.67 mmol) in tetrahydrofuran (20 mL) was treated with ammonium formate (0.30 g, 5.01 mmol) and a catalytic amount of 20% palladium hydroxide on carbon at 60°C for 2 hours. The reaction was filtered through diatomaceous earth and the filtrate concentrated under reduced pressure to provide the title compound (0.30 g, 100%).

Example 457C

3-[bis(methylsulfanyl)methylene]-1-isopentyl-2,4(1*H*,3*H*)-pyridinedione

The product of Example 457B (2.24 g, 12.37 mmol) in pyridine (8.0 mL, 98.96

mmol) and dioxane (50 mL) at 90°C was treated with excess tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi), stirred at 90°C for 1.5 hours and cooled to about 25°C. The reaction solution was decanted from the resulting solids and the solvent was removed under reduced pressure. The residue was dissolved in hexanes and loaded onto a pad of silica gel (300 mL) and eluted with hexane followed by dichloromethane then 25% ethyl acetate in dichloromethane to provide the title compound (2.42 g, 75%).

Example 457D

3-(7-amino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-isopentyl-2(1H)-pyridinone

The product of Example 457C (2.08 g, 7.29 mmol) was treated with the product of Example 414A (2.00 g, 6.96 mmol) in dioxane (20 mL) at 115°C for 30 minutes, cooled to 25°C and concentrated under reduced pressure. A solution of the residue in 4M hydrochloric acid in dioxane (20 mL) was stirred at 25°C for 18 hours and concentrated under reduced pressure. The residue was triturated with dichloromethane and filtered to give the title compound. The filtrate containing the protected intermediate was concentrated and purified by chromatography on silica gel eluting with 1% methanol in dichloromethane. The protected product was re-subjected to the above deprotection conditions to provide the title compound as its hydrochloride salt (2.02 g, 96%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (s, 3 H) 0.94 (s, 3 H) 1.58 (m, 3 H) 3.99 (m, 2 H) 6.31 (d, J=7.35 Hz, 1 H) 6.96 (m, 2 H) 7.34 (d, J=8.46 Hz, 1 H) 8.04 (d, J=7.35 Hz, 1 H) 14.04 (s, 1 H) 14.19 (s, 1 H). MS (ESI-) m/z 375 (M-H)⁺.

Example 457E

benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide

A solution of chlorosulfonylisocyanate (61.8 mg, 0.436 mmol) and benzyl alcohol (47.0 mg, 0.436 mmol) in dichloromethane (7.5 mL) was stirred at 25°C for 1 hour followed by the addition of a solution of the product of Example 457D (150 mg, 0.363 mmol) and triethylamine (183.7 mg, 1.82 mmol) in dichloromethane (14 mL), stirred at 25°C for 20 hours, and partitioned between dichloromethane (25 mL) and 1N aqueous hydrochloric acid (25 mL). The organic layer was separated and dried over magnesium sulfate, filtered and concentrated under reduced pressure to provide the title compound (200 mg, 93%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.93 (s, 3 H) 0.95 (s, 3 H) 1.58 (m, 3 H) 4.00 (m, 2 H) 5.11 (s, 2 H) 6.35 (d, J=7.72 Hz, 1 H) 7.32 (m, 5 H) 7.46 (dd, J=9.01, 2.39 Hz, 1 H) 7.61 (d, J=2.57 Hz, 1 H) 7.65 (d, J=9.19 Hz, 1 H) 8.09 (d, J=7.72 Hz, 1 H) 11.10 (s, 1 H) 12.14 (s, 1 H) 13.87 (s, 1

H) 14.25 (s, 1 H). MS (ESI-) m/z 588 (M-H)⁺.

Example 458N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide

5 A solution of the product of Example 457E (40 mg, 0.068 mmol) in methanol (5 mL) was stirred with 10% palladium on carbon (22 mg) under hydrogen atmosphere at 25°C for 4 hours. The reaction was filtered and the filtrate concentrated under reduced pressure to provide the title compound (28 mg, 99%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.92 (s, 3 H) 0.94 (s, 3 H) 1.58 (m, 3 H) 3.98 (m, 2 H) 6.32 (d, J=4.41 Hz, 1 H) 7.36 (s, 2 H) 7.47 (m, 1 H) 10 7.60 (m, 2 H) 8.06 (s, 1 H) 10.00 (s, 1 H) 13.97 (s, 1 H) 14.23 (s, 1 H). MS (ESI-) m/z 454 (M-H)⁺.

Example 459 A

15 tert-butyl 2-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]ethylcarbamate

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added tert-butyl N-(2-aminoethyl) carbamate (0.016 g, 0.016 mL, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C.

20 The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (6.3 mg, 20%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.34 (s, 9 H) 1.58 (m, 2 H) 1.68 (m, 1 H) 2.88 (m, 2 H) 2.97 (m, 2 H) 4.50 (m, 2 H) 6.75 (s, 1 H) 25 7.50 (m, 2 H) 7.60 (d, J=2.21 Hz, 1 H) 7.72 (d, J=8.82 Hz, 1 H) 7.87 (t, J=5.70 Hz, 1 H) 8.57 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.41, 1.84 Hz, 1 H) 10.26 (s, 1 H) 14.09 (s, 1 H). MS (ESI-) m/z 648 (M-H)⁺.

Example 459B

30 N-(2-aminoethyl)-N'-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide

A solution of the product of Example 459A (0.0053 g, 0.0082 mmol) in a solution of hydrogen chloride in 1,4-dioxane (4 N, 3 mL) and stirred at 25°C and stirred for 18 hours. The solvent was removed under reduced pressure to give the title compound as the 35 hydrochloride salt (4 mg, 89%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.56 (m, 2 H) 1.68 (m, 1 H) 2.89 (m, 2 H) 3.10 (m, 2 H) 4.49 (m, 2 H) 7.51 (m, 2 H) 7.62 (d, J=2.21 Hz, 1 H) 7.74 (d, J=8.82 Hz, 1 H) 7.79 (s, 2 H) 8.03 (t, J=5.70 Hz, 1 H) 8.56 (dd,

$J=7.72$, 1.84 Hz, 1 H) 8.89 (dd, $J=4.41$, 1.84 Hz, 1 H) 10.37 (s, 1 H) 14.16 (s, 1 H). MS (ESI-) m/z 548 (M-H)⁻.

Example 460

ethyl 1-({[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]amino}sulfonyl)-3-piperidinecarboxylate

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was added ethyl nipecotate (0.016 g, 0.016 mL, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours, and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (20.3 mg, 63%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.98 (d, $J=6.62$ Hz, 6 H) 1.15 (t, $J=7.17$ Hz, 3 H) 1.45 (m, 2 H) 1.56 (m, 2 H) 1.68 (m, 2 H) 1.82 (m, 1 H) 2.88 (m, 1 H) 3.04 (m, 1 H) 3.63 (m, 1 H) 4.02 (m, 2 H) 4.49 (m, 2 H) 7.51 (dd, $J=9.01$, 2.39 Hz, 2 H) 7.57 (d, $J=2.21$ Hz, 1 H) 7.70 (d, $J=8.46$ Hz, 1 H) 8.56 (dd, $J=8.09$, 1.84 Hz, 1 H) 8.88 (d, $J=3.68$ Hz, 1 H) 10.52 (s, 1 H) 14.13 (s, 1 H). MS (ESI-) m/z 645 (M-H)⁻.

Example 461A

methyl (2*S*)-1-(chlorosulfonyl)-2-pyrrolidinecarboxylate

A solution of L-proline methyl ester hydrochloride (0.33 g, 0.002 mole) in toluene (5 mL), dichloromethane (2 mL) and triethylamine (0.6 mL, 0.004 mole) was added dropwise over a period of 3 minutes to a cold (-20°C) solution of sulfonyl chloride (0.32 mL, 0.0039 mole) in toluene. The mixture was stirred an additional 45 minutes at -20°C. The reaction was filtered and the solvent was removed under reduced pressure to give the title compound (0.40 g). ¹H NMR (300 MHz, CDCl₃) δ 2.13 (m, 2 H) 2.32 (m, 2 H) 3.58 (m, 1 H) 3.75 (m, 1 H) 3.79 (s, 3 H) 4.40 (dd, $J=8.82$, 4.04 Hz, 1 H).

Example 461B

methyl (2*S*)-1-({[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]amino}sulfonyl)-2-pyrrolidinecarboxylate

The product of Example 205 (0.030g, 0.0703 mmol) in acetonitrile (2 mL) was treated with the product of Example 461A (0.018 g, 0.077 mmol) and triethylamine (0.011 mL, 0.077 mmol), stirred at 60°C for 20 hours and cooled to about 25°C. The solvent was evaporated under reduced pressure, and the residue was purified by reverse phase preparative

HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (7 mg, 16%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.25 Hz, 6 H) 1.59 (m, 2 H) 1.67 (m, 2 H) 1.87 (m, 4 H) 2.09 (d, J=8.46 Hz, 1 H) 3.60 (s, 3 H) 4.26 (dd, J=8.64, 3.86 Hz, 1 H) 4.50 (m, 2 H) 7.55 (m, 4 H) 7.73 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.78, 1.84 Hz, 1 H) 10.53 (s, 1 H) 14.07 (s, 1 H). MS (ESI-) m/z 617 (M-H).

Example 462

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-pyrrolidinesulfonamide

The product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was treated with pyrrolidine (0.0076 g, 0.009 mL, 0.1 mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (2.6 mg, 9%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.98 (d, J=6.25 Hz, 6 H) 1.23 (s, 1 H) 1.55 (s, 1 H) 1.75 (m, 1 H) 2.51 (m, 4 H) 3.21 (t, J=6.62 Hz, 4 H) 4.48 (s, 2 H) 7.60 (s, 6 H) 8.53 (s, 1 H) 8.87 (s, 1 H) 10.35 (s, 1 H). MS (ESI-) m/z 559 (M-H).

Example 4633-hydroxy-N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-piperidinesulfonamide

To the product of Example 435B (0.029 g, 0.05 mmol) in acetonitrile (2 mL) was treated with 3-hydroxypiperidine hydrochloride (0.0079 g, 0.1 mmol) and triethylamine (0.00796 mL, 0.057mmol). The reaction mixture was heated in a microwave reactor at 80°C for 2 hours and cooled to about 25°C. The solvent was removed under a stream of warm nitrogen, and the residue was purified by reverse phase preparative HPLC on a Waters Symmetry C8 column (25mm x 100mm, 7 μ m particle size) using a gradient of 10% to 100% acetonitrile/10mM ammonium acetate in water over 8 minutes (10 minutes run time) at a flow rate of 40mL/min give the title compound (4.8 mg, 18%). ¹H NMR (300 MHz, DMSO-d₆) δ 0.99 (d, J=6.62 Hz, 6 H) 1.18 (s, 1 H) 1.35 (s, 1 H) 1.59 (m, 2 H) 1.67 (d, J=34.56 Hz, 2 H) 2.71 (s, 4 H) 3.51 (s, 4 H) 4.50 (m, 2 H) 7.51 (m, 2 H) 7.58 (m, 1 H) 7.72 (d, J=8.82 Hz, 1 H) 8.57 (dd, J=8.09, 1.84 Hz, 1 H) 8.90 (dd, J=4.60, 1.65 Hz, 1 H) 10.46 (s, 1 H) 14.08 (s, 1 H). MS (ESI-) m/z 589 (M-H).

Example 464A

tert-butyl 3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinoliny]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-ylcarbamate

A mixture of the product of Example 432B (1.25 g, 3.74 mmol) and the product of Example 414A (1.06 g, 3.7 mmol) in anhydrous dioxane (50 mL) was heated at reflux for 3 hours, cooled to 25°C, and concentrated under reduced pressure. The residue was triturated in hot 3:1 hexane/ethyl acetate (30 mL), cooled, and the solid was collected by filtration and dried to provide the title compound (1.5 g, 76% yield).

Example 464B

3-(7-amino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(cyclobutylamino)-4-hydroxy-2(1H)-quinolinone

A slurry of the product of Example 464A (1.5 g, 2.85 mmol) in dichloromethane (10 mL) at 0°C was treated dropwise with 6 mL of trifluoroacetic acid, stirred at 25°C for 2 hours and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with 10% aqueous sodium bicarbonate (3 x 50 mL), washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound (1.1 g, 91% yield).

Example 464C

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinoliny]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}ethanesulfonamide

A solution of the product of Example 464B (0.0425 g, 0.1 mmol) in pyridine (300 µL) was treated dropwise with ethane sulfonyl chloride (0.026 mg, 0.2 mmol), stirred for 1 hour at 25°C and concentrated under reduced pressure. The residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 8min (10min run time) at a flow rate of 40 mL/minute to provide the title compound (0.020 g, 39% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 1.23 (t, J=7.17 Hz, 3 H) 1.56 (m, 1 H) 1.70 (m, 1 H) 2.05 (m, 4 H) 3.19 (q, J=7.35 Hz, 2 H) 3.77 (m, 1 H) 6.56 (s, 1 H) 7.44 (t, J=7.54 Hz, 1 H) 7.60 (dd, J=8.82, 2.21 Hz, 1 H) 7.67 (m, 2 H) 7.89 (m, 1 H) 8.06 (d, J=8.46 Hz, 1 H) 8.17 (d, J=8.09 Hz, 1 H) 10.33 (s, 1 H) 14.16 (s, 1 H) 15.03 (br. s., 1 H). MS (ESI) m/z 516 (M-H)⁺.

Example 465 benzyl 3-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinoliny]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}diazathiane-1-carboxylate 2,2-dioxide

A solution of chlorosulfonyl isocyanate (0.051 g, 0.36 mmol) in dichloromethane (2 mL) was treated dropwise with benzyl alcohol (0.039 g, 0.36 mmol) at 0°C, stirred at 25°C

for 30 minutes and treated with a solution of the product of Example 464B (0.127 g, 0.03 mmol) and triethylamine (0.12 g, 1.2 mmol) in dichloromethane (4 mL). The reaction mixture was stirred for 2 hours at 25°C and partitioned between dichloromethane (10 mL) and 1N aqueous hydrochloric acid (10 mL). The resulting organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting with 3% methanol in dichloromethane to provide the title compound (0.127 g, 66% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 1.57 (m, 1 H) 1.70 (m, 1 H) 2.04 (m, 4 H) 3.78 (m, 1 H) 5.12 (s, 2 H) 6.57 (s, 1 H) 7.30 (m, 5 H) 7.44 (t, J=7.54 Hz, 1 H) 7.50 (m, 1 H) 7.66 (m, 2 H) 7.89 (t, J=7.91 Hz, 1 H) 8.07 (d, J=8.09 Hz, 1 H) 8.17 (d, J=8.46 Hz, 1 H) 11.13 (s, 1 H) 12.16 (s, 1 H) 14.15 (s, 1 H) 15.06 (s, 1 H). MS (ESI) m/z 637 (M-H).

Example 466A

benzyl 3-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-1-methyldiazathiane-1-carboxylate 2,2-dioxide

A solution of the product of Example 465 (0.045 g, 0.07 mmol) in 1:1 tetrahydrofuran/methanol (2 ml) at -10°C was treated dropwise with trimethylsilyl diazomethane (2.0 M in hexanes, 70 µL, 0.14 mmol), stirred at 25°C for 16 hours and concentrated under reduced pressure to provide the title compound (0.045 g, 98% yield).

Example 466B

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-N'-methylsulfamide

A solution of the product of Example 466A (0.045 g, 0.069 mmol) in tetrahydrofuran (8 mL) and methanol (2 mL) was treated with 10% palladium on carbon (20 mg) and stirred for 24 hours at 25°C under a hydrogen atmosphere. The resulting solution was filtered through Celite® (diatomaceous earth) and the filtrate concentrated under reduced pressure. The residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 8min (10min run time) at a flow rate of 40 mL/minute to provide the title compound (0.006 g, 17% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 1.55 (m, 1 H) 1.69 (m, 1 H) 2.03 (m, 4 H) 3.78 (m, 1 H) 6.55 (s, 1 H) 7.40 (d, J=5.52 Hz, 1 H) 7.45 (m, 1 H) 7.52 (dd, J=8.82, 2.57 Hz, 1 H) 7.65 (m, 2 H) 7.88 (t, J=7.91 Hz, 1 H) 8.07 (d, J=8.46 Hz, 1 H) 8.16 (d, J=6.99 Hz, 1 H) 10.24 (s, 1 H) 14.11 (s, 1 H) 15.11 (s, 1 H). MS (ESI) m/z 517 (M-H).

Example 467N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}sulfamide A solution of the product of Example 465 (0.790 g, 1.2 mmol) in tetrahydrofuran (80 mL) and methanol (20 mL) was treated with 10% palladium on carbon (200 mg) and stirred for 24 hours at 25°C under a hydrogen atmosphere. The reaction was filtered through Celite® (diatomaceous earth) and

the filtrate concentrated under reduced pressure to provide the title compound (0.500 g, 83% yield). ¹H NMR (300 MHz, DMSO-d₆) δ 1.58 (m, 1 H) 1.67 (m, 1 H) 2.03 (m, 4 H) 3.78 (m, 1 H) 6.56 (s, 1 H) 7.39 (s, 2 H) 7.44 (t, J=7.54 Hz, 1 H) 7.52 (m, 1 H) 7.64 (m, 2 H) 7.89 (t, J=7.91 Hz, 1 H) 8.07 (d, J=8.82 Hz, 1 H) 8.17 (d, J=8.46 Hz, 1 H) 10.06 (s, 1 H) 14.09 (s, 1 H) 15.14 (s, 1 H). MS (ESI) m/z 503 (M-H)⁺.

Example 468A

4-(benzyloxy)-1-(cyclobutylmethyl)-2(1H)-pyridinone

A solution of 4-benzyloxy-1H-pyridin-2-one (0.60 g, 2.98 mmol) in *N,N*-dimethylacetamide (10 mL) at 0°C was treated with sodium hydride (0.086 g, 3.58 mmol) for 30 min, then bromomethyl cyclobutane (0.40 mL, 3.58 mmol) was added and the mixture was stirred at 25°C for 48 hours. The solution was partitioned between 10% aqueous ammonium chloride solution and dichloromethane, the organic layer was separated, concentrated under reduced pressure and the residue was chromatographed on silica gel, eluting with 1% methanol in dichloromethane to provide the title compound (0.426 g, 53%).

Example 468B

1-(cyclobutylmethyl)-4-hydroxy-2(1H)-pyridinone

A solution of the product of Example 468A (0.426 g, 1.58 mmol) in tetrahydrofuran (20 mL) was treated with ammonium formate (0.38 g, 6.03 mmol) and a catalytic amount of 20% palladium hydroxide on carbon at 70°C for 2 hours. The reaction mixture was cooled to about 25°C, filtered through diatomaceous earth and the filtrate concentrated under reduced pressure to provide the title compound (0.244 g, 86%).

Example 468C

3-[bis(methylsulfanyl)methylene]-1-(cyclobutylmethyl)-2,4(1H,3H)-pyridinedione

A solution of the product of Example 468B (0.244 g, 1.36 mmol) and pyridine (0.88 mL, 10.89 mmol) in dioxane (6 mL) was treated with excess tris(methylthio)methyl methyl sulfate (prepared using the procedures in *Synthesis*, 22-25, 1988; M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi), stirred at 90°C for 1.5 hours, and cooled to about 25°C. The reaction solution was decanted from the resulting solids and the solvent was removed under a stream of warm nitrogen. The residue was dissolved in hexanes and loaded onto a 2 g Alltech Seppack and eluted with hexanes followed by dichloromethane followed by 25% ethyl acetate in dichloromethane to provide the title compound (0.192 g, 50%).

Example 468D*N*-{3-[1-(cyclobutylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-3-pyridinyl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

A solution of the product of Example 468C (0.050 g, 0.176 mmol) in dioxane (5 mL) was treated with the product of Example 425D (0.030 g, 0.113 mmol), stirred at 110°C for 1 hour, and cooled to 25°C. The solid precipitate was collected by filtration and dried to provide the title compound (0.018 g, 35%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.88 (m, 6 H) 2.74 (dt, *J*=15.17, 7.68 Hz, 1 H) 3.08 (s, 3 H) 4.03 (d, *J*=7.35 Hz, 2 H) 6.32 (d, *J*=7.72 Hz, 1 H) 7.56 (dd, *J*=8.82, 2.57 Hz, 1 H) 7.62 (d, *J*=2.21 Hz, 1 H) 7.66 (m, 1 H) 8.06 (d, *J*=7.35 Hz, 1 H) 10.24 (s, 1 H) 13.83 (s, 1 H) 14.28 (s, 1 H). MS (ESI-) *m/z* 451 (M-H)⁻.

Example 469*N*-{3-[5-bromo-1-(cyclobutylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-3-pyridinyl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}methanesulfonamide

A solution of the product of Example 468D (0.030 g, 0.066 mmol) in tetrahydrofuran (2 mL) was treated with 1,3-dibromo-5,5-dimethyl-hydantoin (0.015 g, 0.052 mmol) at 25°C for 18 hours. The reaction was concentrated under a warm stream of nitrogen and the residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7μm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 8min (10min run time) at a flow rate of 40mL/min to provide the title compound (0.008 g, 23%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.83 (m, 4 H) 1.95 (m, 2 H) 2.75 (m, 1 H) 3.08 (s, 3 H) 4.03 (d, *J*=6.99 Hz, 2 H) 7.56 (dd, *J*=9.01, 2.39 Hz, 1 H) 7.62 (d, *J*=2.21 Hz, 1 H) 7.67 (d, *J*=8.82 Hz, 1 H) 8.55 (s, 1 H) 10.24 (s, 1 H) 14.35 (s, 1 H). MS (ESI-) *m/z* 530 (M-H)⁻.

Example 470A*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]methanesulfonamide

A solution of the product of Example 457C (0.195 g, 0.68 mmol) in dioxane (10 mL) was reacted with the product of Example 425D (0.17 g, 0.64 mmol) at 115°C for 1 hour. After cooling to about 25°C, the solid precipitate was collected by filtration and dried to provide the title compound (0.258 g, 89%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.93 (d, *J*=6.25 Hz, 6 H) 1.58 (m, 3 H) 3.08 (s, 3 H) 3.99 (m, 2 H) 6.33 (d, *J*=6.62 Hz, 1 H) 7.57 (m, 2 H) 7.67 (d, *J*=8.82 Hz, 1 H) 8.07 (d, *J*=6.62 Hz, 1 H) 10.25 (s, 1 H) 13.84 (s, 1 H) 14.28 (s, 1 H). MS (ESI-) *m/z* 453 (M-H)⁻.

Example 470B*N*-[3-(5-bromo-4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]methanesulfonamide

A solution of the product of Example 470A (0.258 g, 0.57 mmol) in tetrahydrofuran (10 mL) was treated with 1,3-dibromo-5,5-dimethyl hydantoin (0.24 g, 0.84 mmol) at 25°C for 18 hours. The solvent was under a warm stream of nitrogen and the residue was chromatographed on silica gel eluting with dichloromethane to provide the title compound (0.13 g, 43%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.94 (d, J=6.25 Hz, 6 H) 1.61 (m, 3 H) 3.08 (s, 3 H) 4.00 (m, 2 H) 7.56 (dd, J=8.82, 2.21 Hz, 1 H) 7.63 (d, J=2.21 Hz, 1 H) 7.70 (m, 1 H) 8.59 (s, 1 H) 10.26 (s, 1 H) 14.29 (s, 1 H). MS (ESI-) *m/z* 532 (M-H)⁻.

Example 470C*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-5-vinyl-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]methanesulfonamide

The product of Example 470B (0.027 g, 0.051 mmol) and tributyl(vinyl)tin (0.015 mL, 0.051 mmol) in tetrahydrofuran and a catalytic amount of dichlorobis(triphenyl phosphine)palladium(II) were reacted at 75°C for 20 hours. The solution was cooled to about 25°C and concentrated. The residue was purified by preparative HPLC on a Waters Symmetry C8 column (25mm X 100mm, 7µm particle size) using a gradient of 10% to 100% acetonitrile:0.1% aqueous TFA over 8min (10min run time) at a flow rate of 40mL/min to provide the title compound (0.005 g, 21%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.95 (d, J=5.88 Hz, 6 H) 1.61 (m, 3 H) 3.08 (s, 3 H) 4.05 (m, 2 H) 5.32 (d, J=11.03 Hz, 1 H) 5.87 (d, J=18.02 Hz, 1 H) 6.64 (m, 1 H) 7.64 (m, 3 H) 8.42 (s, 1 H) 10.26 (s, 1 H) 14.42 (s, 1 H) 14.67 (s, 1 H). (ESI-) *m/z* 479 (M-H)⁻.

Example 471*N*-(2-furylmethyl)-3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxamide 2,2-dioxide

A solution of chlorosulfonyl isocyanate (4.9 µL, 0.0562 mmol) in dichloromethane (2 mL) was treated dropwise with furfurylamine (5 µL, 0.0562 mmol) at 25°C, stirred at 25°C for 30 min, treated with a solution of product of Example 205 (20 mg, 0.0468 mmol) and triethylamine (26 µL, 0.187 mmol) in dichloromethane (2 mL) and stirred for 24 hours at 25°C. The reaction mixture was partitioned between dichloromethane (10 mL) and 1N aqueous hydrochloric acid (10 mL). The resulting organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the title compound (15%). MS *m/z* 630 (M+H)⁺.

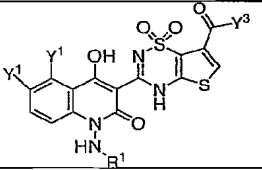
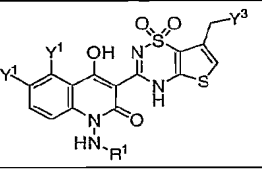
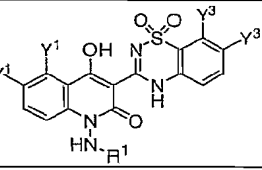
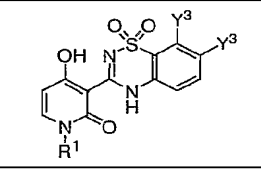
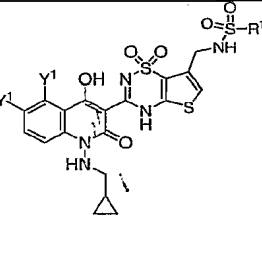
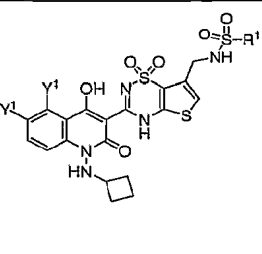
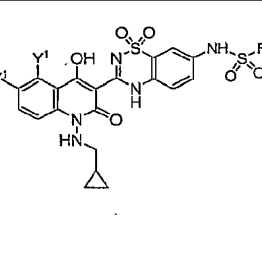
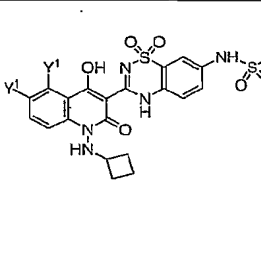
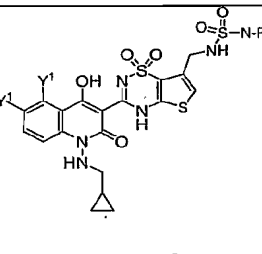
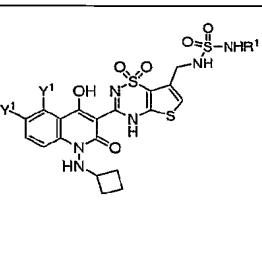
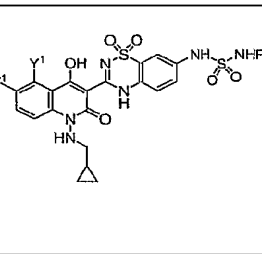
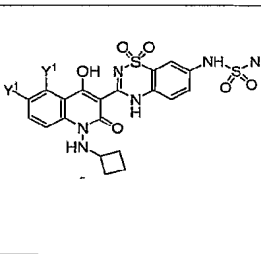
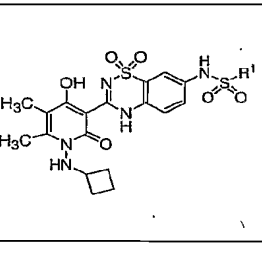
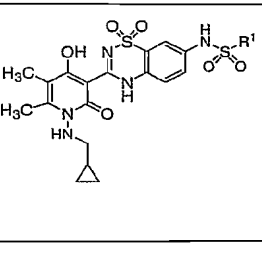
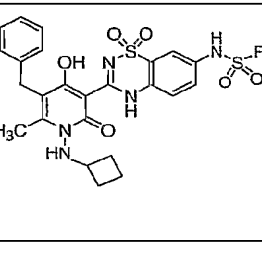
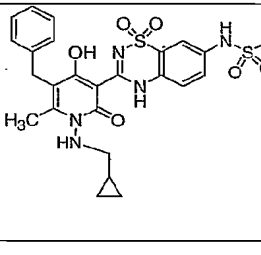
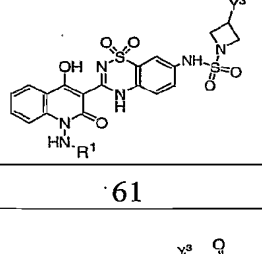
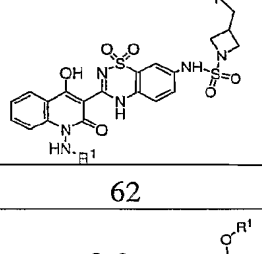
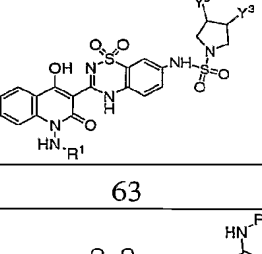
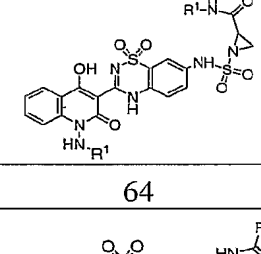
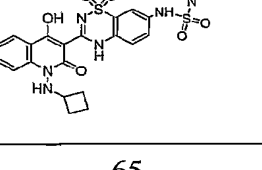
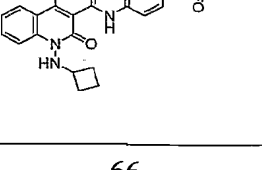
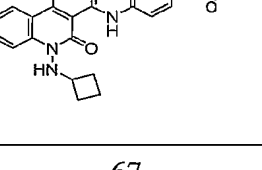
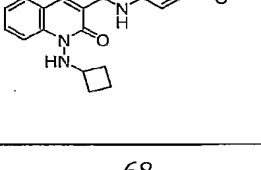
The following additional compounds of the present invention, can be prepared by one

skilled in the art using known synthetic methodology or by using synthetic methodology described in the Schemes and Examples contained herein. The additional compounds encompassed by the following tables can be described by taking one core from Table 1, one R¹ substituent from Table 2 (wherein X₁ represents the Core Ring Structure), one or two Y³ substituent from Table 4, and when needed Y₁ and/or Y₂ substituent from Table 3.

Table 1: Examples of Core Ring Structures

1	2	3	4
5	6	7	8
9	10	11	12
13	14	15	16
17	18	19	20

21	22	23	24
25	26	27	28
29	30	31	32
33	34	35	36
37	38	39	40
41	42	43	44

			
45	46	47	48
			
49	50	51	52
			
53	54	55	56
			
57	58	59	60
			
61	62	63	64
			
65	66	67	68

69	70	71	72
73	74	75	76
77	78	79	80
81	82	83	84
85	86	87	88
89	90	91	92

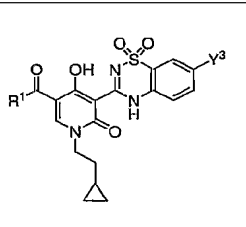
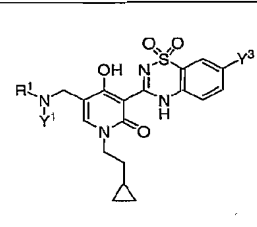
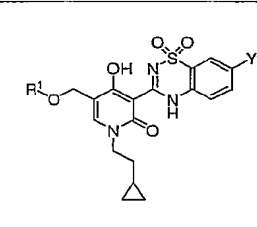
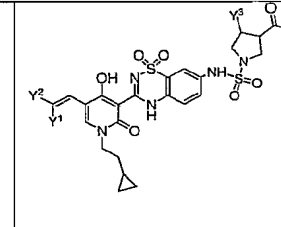
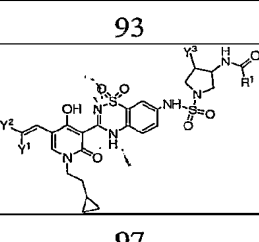



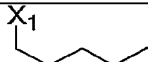
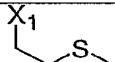
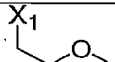

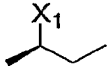
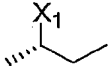


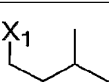

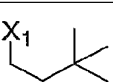
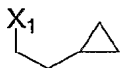
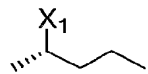
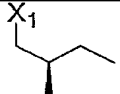
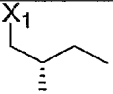
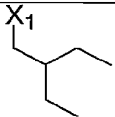
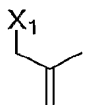
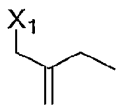
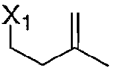

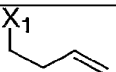
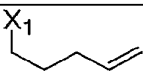
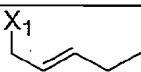
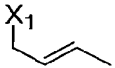

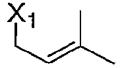
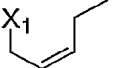
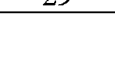

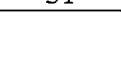
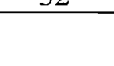







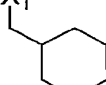




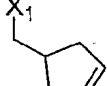
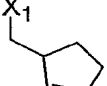
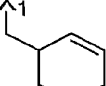
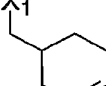
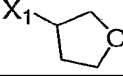
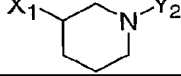
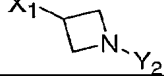
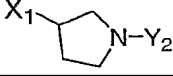
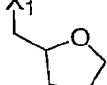
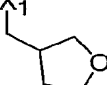
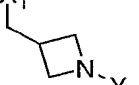
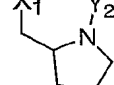
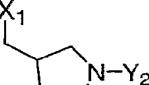
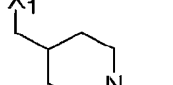
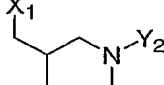
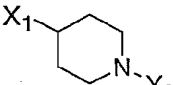
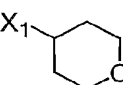
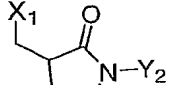
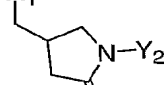
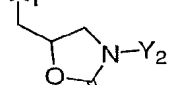
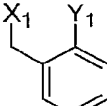
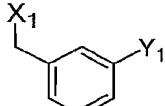
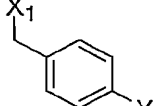
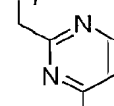
 <p>93</p>	 <p>94</p>	 <p>95</p>	 <p>96</p>
 <p>97</p>	<p>98</p>	<p>99</p>	<p>100</p>

Table 2: Examples of R¹ Substituents

X_1-H	X_1-CH_3	X_1 	X_1 
1 	2 	3 	4 
5 	6 	7 	8 
9 	10 	11 	12 
13 	14 	15 	16 
17 	18 	19 	20 
21 	22 	23 	24 
25 	26 	27 	28 
29 	30 	31 	32 

			
33	34	35	36
			
37	38	39	40
			
41	42	43	44
			
45	46	47	48
			
49	50	51	52
			
53	54	55	56
			
57	58	59	60
			
61	62	63	64
			
65	66	67	68

69	70	71	72
73	74	75	76
77	78	79	80
81	82	83	84
85	86	87	88
89	90	91	92
93	94	95	96
97	98	99	100

101	102	103	104
105	106	107	108
109	110	111	112
113	114	115	116
117	118	119	120
121	122	123	124
125	126	127	128
129	130	131	132
133	134	135	136

137	138	139	140
141	142	143	144
145	146	147	148
149	150	151	152
153	154	155	156
157	158	159	160
161	162	163	164
165	166	167	168

Table 3: Substituents of Y₁ and Y₂

H	CH ₃	-CH ₂ CH ₃	-CH(CH ₃) ₂
-F	-Cl	-Br	NO ₂
-CN	-OCH ₃	-NHCH ₃	-N(CH ₃) ₂
-NH ₂	-OH	-C(O)NH ₂	-NC(O)NH ₂
Y ₂			
H	CH ₃	-CH ₂ CH ₃	-CH(CH ₃) ₂
-COCH ₃	-CO ₂ CH ₃	CO ₂ CH ₃	-NC(O)NH ₂

-NH ₂	-OH	-C(O)NH ₂	
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Table 4: Examples of Y₃

X ₁ -H	X ₁ -CH ₃	X ₁ -OH	X ₁ -NH ₂
1 	2 	3 	4
5 	6 	7 	8
9 	10 	11 	12
13 	14 	15 	16
17 	18 	19 	20
21 	22 	23 	24
25 	26 	27 	28
29 	30 	31 	32
33 	34 	35 	36
37	38	39	40

41	42	43	44
45	46	47	48
49	50	51	52
53	54	55	56
57	58	59	60
61	62	63	64
65	66	67	68
69	70	71	72
73	74	75	76

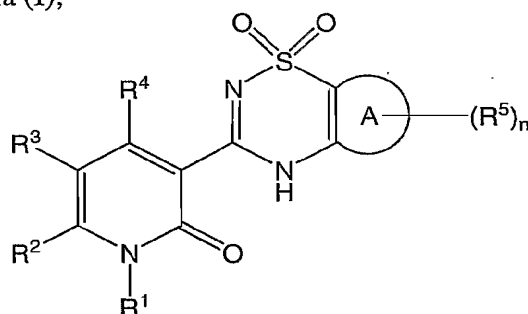
72	73	74	75
76	77	78	79
80	81	82	83
84	85	86	87
88	89	90	91
92	93	94	95
96	97	98	100
101	102	103	104
105	106	107	108
109	110	111	112

113	114	115	116

It will be evident to one skilled in the art that the present invention is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

WHAT IS CLAIMED IS

1. A compound of formula (I),



(I)

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

A is a monocyclic or bicyclic ring selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocycle;

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-, R_aR_bNC(O)NR_calkyl-, R_fR_gC=N- and R_kO-, wherein R¹ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_e), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_e), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_e;

R² and R³ are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, -N(R_a)(R_b), R_aR_bNC(O)-, -SR_a, -S(O)R_a, -S(O)₂R_a and R_aC(O)-; wherein R² and R³ are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a, alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, -(alkyl)(OR_k), -(alkyl)(NR_aR_b), -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b;

alternatively, R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is independently substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$,

$R_c R_d \text{NalkylC(O)-}$, $R_c R_d \text{NC(O)-}$, $R_c R_d \text{NC(O)Oalkyl-}$, $R_c R_d \text{NC(O)N(R}_e\text{)alkyl-}$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c \text{R}_d)$, $-\text{SR}_c$, $-\text{S(O)R}_c$, $-\text{S(O)}_2 \text{R}_c$, $-\text{OR}_c$, $-\text{N(R}_c\text{)(R}_d)$, $-\text{C(O)R}_c$, $-\text{C(O)OR}_c$ and $-\text{C(O)NR}_c \text{R}_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c \text{R}_d)$, $-\text{alkylSO}_2 \text{NR}_c \text{R}_d$, $-\text{alkylC(O)NR}_c \text{R}_d$, $-\text{SR}_c$, $-\text{S(O)R}_c$, $-\text{S(O)}_2 \text{R}_c$, $-\text{OR}_c$, $-\text{N(R}_c\text{)(R}_d)$, $-\text{C(O)R}_c$, $-\text{C(O)OR}_c$ and $-\text{C(O)NR}_c \text{R}_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-\text{NR}_f \text{R}_h$, $-\text{OR}_f$, $-\text{CO(R}_f)$, $-\text{SR}_f$, $-\text{SOR}_f$, $-\text{SO}_2 \text{R}_f$, $-\text{C(O)NR}_f \text{R}_h$, $-\text{SO}_2 \text{NR}_f \text{R}_h$, $-\text{C(O)OR}_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f \text{R}_h)$, $-\text{SR}_f$, $-\text{S(O)R}_f$, $-\text{S(O)}_2 \text{R}_f$, $-\text{OR}_f$, $-\text{N(R}_f\text{)(R}_h)$, $-\text{C(O)R}_f$, $-\text{C(O)OR}_f$, $-\text{C(O)NR}_f \text{R}_h$, $-\text{C(O)N(H)NR}_f \text{R}_h$, $-\text{N(R}_e\text{)C(O)OR}_f$, $-\text{N(R}_e\text{)SO}_2 \text{NR}_f \text{R}_h$, $-\text{N(R}_e\text{)C(O)NR}_f \text{R}_h$, $-\text{alkylN(R}_e\text{)C(O)OR}_f$, $-\text{alkylN(R}_e\text{)SO}_2 \text{NR}_f \text{R}_h$, and $-\text{alkylN(R}_e\text{)C(O)NR}_f \text{R}_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f \text{R}_h)$, $-\text{SR}_f$, $-\text{S(O)R}_f$, $-\text{S(O)}_2 \text{R}_f$, $-\text{OR}_f$, $-\text{N(R}_f\text{)(R}_h)$, $-\text{C(O)R}_f$, $-\text{C(O)OR}_f$ and $-\text{C(O)NR}_f \text{R}_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f, R_g and R_h, at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl), -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂, -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

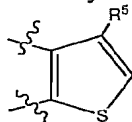
alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-, R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-, R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, 3, or 4;

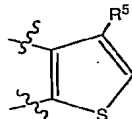
with the proviso that when A is a monocyclic ring other than



5

and R^4 is alkoxy, aryloxy, hydroxy or R_eS- , and R^5 is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aSO_2N(R_f)-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_aR_bNSO_2-$ or $-OR_k$, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl;

and with the further proviso that when A is



15

and R^4 is hydroxy or R_eS- , and R^5 is hydrogen, unsubstituted alkyl, halo or $-OR_k$, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

20

2. The compound of claim 1 wherein A is a monocyclic ring selected from the group consisting of aryl and heteroaryl.

25

3. The compound of claim 2 wherein

A is aryl; and

R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyridazinyl, thienyl, furanyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, tetrazolyl, cyclopentyl and cyclohexyl.

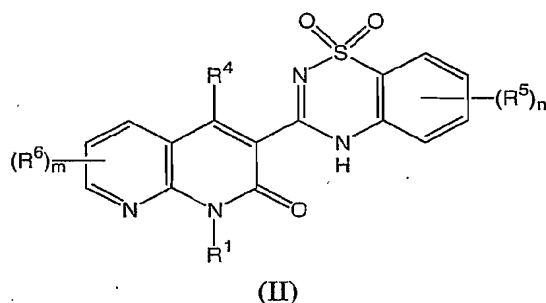
30

4. The compound of claim 3 wherein A is phenyl.

5. The compound of claim 4 wherein R₂ and R₃ together with the carbon atoms to which they are attached form a pyridyl ring.

5

6. The compound of claim 1 of formula (II)



10 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-, R_aR_bNC(O)NR_calkyl-, R_fR_gC=N- and R_kO-, wherein R¹ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_e), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_e), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_e;

25 R⁴ is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN-, N₃-, R_eS-, wherein R⁴ is independently substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, -OH, -NH₂, and -COOH;

30 R⁵ is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl,

hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$,
 $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$,
 $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$,
 $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is
 5 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl,
 heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$,
 $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and
 $-C(O)NR_cR_d$;

10

R^6 is independently selected at each occurrence from the group consisting of alkyl,
 alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$,
 $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is
 15 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$,
 $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting
 20 of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl,
 cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl,
 haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl,
 heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$,
 $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$,
 25 $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and
 R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$,
 $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

30

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached
 form a three- to six-membered ring selected from the group consisting of heteroaryl and
 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2
 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 35 oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-alkylSO_2NR_cR_d$,
 $-alkylC(O)NR_cR_d$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and

-C(O)NR_cR_d;

R_c and R_d, at each occurrence, are independently selected from the group consisting of hydrogen, -NR_fR_h, -OR_f, -CO(R_f), -SR_f, -SOR_f, -SO₂R_f, -C(O)NR_fR_h, -SO₂NR_fR_h,
 5 -C(O)OR_f, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 10 heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_h, -C(O)N(H)NR_fR_h, -N(R_e)C(O)OR_f, -N(R_e)SO₂NR_fR_h, -N(R_e)C(O)NR_fR_h, -alkylN(R_e)C(O)OR_f, -alkylN(R_e)SO₂NR_fR_h, and -alkylN(R_e)C(O)NR_fR_h;

15 alternatively, R_c and R_d, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 20 heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f and -C(O)NR_fR_h;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

25 R_f, R_g and R_h, at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 30 cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl), -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂, -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

35 alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl,

cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bN alkyl-, R_aO alkyl-, $R_aR_bNC(O)$ -, $R_aR_bNC(O)$ alkyl, R_aS -, $R_aS(O)$ -, R_aSO_2 -, R_aS alkyl-, $R_a(O)S$ alkyl-, R_aSO_2 alkyl-, $R_aOC(O)$ -, $R_aOC(O)$ alkyl-, $R_aC(O)$ -, $R_aC(O)$ alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, 3, or 4;

with the proviso that when R^4 is alkoxy, aryloxy, hydroxy or R_eS -, and R^5 is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, R_aR_bN -, $R_aC(O)$ -, R_aS -, $R_a(O)S$ -, $R_a(O)_2S$ -, $R_aSO_2N(R_f)$ -, $R_aR_bNC(O)$ -, $R_kOC(O)$ -, $R_aR_bNSO_2$ - or -OR_k, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

7. The compound of claim 6 wherein R^4 is hydroxy.

8. The compound of claim 7 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkenyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_fR_gC=N-$ and R_kO- .
9. The compound of claim 5 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:
- 1-[2-(1-cyclohexen-1-yl)ethyl]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- ethyl [3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2-oxo-1,8-naphthyridin-1(2H)-yl]acetate;
- 1-(3-anilinopropyl)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 3-[3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2-oxo-1,8-naphthyridin-1(2H)-yl]propanal;
- 1-[3-(dimethylamino)propyl]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 1-{3-[[2-(dimethylamino)ethyl](methyl)amino]propyl}-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 1-(2-aminoethyl)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 1-[3-(diethylamino)propyl]-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 1-(benzyloxy)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 1-(benzyloxy)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1,8-naphthyridin-2(1H)-one;
- 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-isobutoxy-1,8-naphthyridin-2(1H)-one;
- 1-benzyl-4-chloro-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;
- 1-butyl-4-chloro-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;
- 4-amino-1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-(methylamino)-1,8-naphthyridin-2(1H)-one;

1-butyl-4-(dimethylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;

5 1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydrazino-1,8-naphthyridin-2(1H)-one;

4-azido-1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-[(2-hydroxyethyl)amino]-1,8-naphthyridin-2(1H)-one;

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-*N'*-(2-phenylethyl)sulfamide;

benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

15 *N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-propyldiazathiane-1-carboxylate 2,2-dioxide;

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-*N'*-propylsulfamide;

methyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

allyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

25 2-propynyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

2-cyanoethyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

2-(trimethylsilyl)ethyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

methyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

35 benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-methyldiazathiane-1-carboxylate 2,2-dioxide;

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-*N'*-methylsulfamide;

2-aminoethyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

N-cyclopentyl-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

5 *N*-cyclobutyl-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-*N'*-(4-piperidinyl)sulfamide;

10 *N*-(2-hydroxyethyl)-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]propanamide;

N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-azetidinesulfonamide;

15 3-hydroxy-*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-azetidinesulfonamide;

3-amino-*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-pyrrolidinesulfonamide;

20 *N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-piperidinesulfonamide;

N-benzyl-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

ethyl 3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]benzoate;

25 3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]benzoic acid;

3-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]amino]benzamide;

30 *N*-(2-aminoethyl)-*N'*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

ethyl 1-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]-3-piperidinecarboxylate;

methyl (2*S*)-1-[(3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)amino)sulfonyl]-2-pyrrolidinecarboxylate;

35 *N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]-1-pyrrolidinesulfonamide;

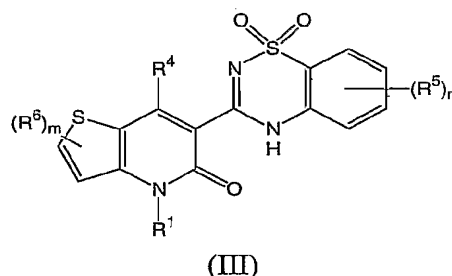
3-hydroxy-*N*-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-

dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]-1-piperidinesulfonamide; and

N-(2-furylmethyl)-3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro[1,8]naphthyridin-3-yl)-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxamide 2,2-dioxide.

10. The compound of claim 4 wherein R^2 and R^3 , together with the carbon atoms to which they are attached form a thienyl ring.

11. The compound of claim 1 of formula (III):



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

- R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

- R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo,

haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$, $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-alkylSO_2NR_cR_d$,

-alkylC(O)NR_cR_d, -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R_c and R_d, at each occurrence, are independently selected from the group consisting of hydrogen, -NR_fR_h, -OR_f, -CO(R_f), -SR_f, -SOR_f, -SO₂R_f, -C(O)NR_fR_h, -SO₂NR_fR_h, -C(O)OR_f, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_h, -C(O)N(H)NR_fR_h, -N(R_e)C(O)OR_f, -N(R_e)SO₂NR_fR_h, -N(R_e)C(O)NR_fR_h, -alkylN(R_e)C(O)OR_f, -alkylN(R_e)SO₂NR_fR_h, and -alkylN(R_e)C(O)NR_fR_h;

alternatively, R_c and R_d, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f and -C(O)NR_fR_h;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f, R_g and R_h, at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl), -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂, -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

alternatively, R_f and R_g together with the carbon atom to which they are attached form

a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached
 5 form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
 10 -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl,
 15 cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bN alkyl-, R_aO alkyl-, $R_aR_bNC(O)$ -, $R_aR_bNC(O)$ alkyl, R_aS -, $R_aS(O)$ -, R_aSO_2 -, R_aS alkyl-, $R_a(O)S$ alkyl-, R_aSO_2 alkyl-, $R_aOC(O)$ -, $R_aOC(O)$ alkyl-, $R_aC(O)$ -, $R_aC(O)$ alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of
 20 alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, or 2; and

25

n is 0, 1, 2, 3, or 4;

with the proviso that when R^4 is alkoxy, aryloxy, hydroxy or R_eS -, and R^5 is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl,
 30 cyano, nitro, R_aR_bN -, $R_aC(O)$ -, R_aS -, $R_a(O)S$ -, $R_a(O)_2S$ -, $R_aSO_2N(R_f)$ -, $R_aR_bNC(O)$ -, $R_kOC(O)$ -, $R_aR_bNSO_2$ - or -OR_k, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl,
 35 heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

12. The compound of claim 11 wherein R^4 is hydroxy.

13. The compound of claim 12 wherein R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_fR_gC=N- and R_kO-.

14. The compound of claim 10 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:

4-amino-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-Dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(isobutylamino)thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3*S*)-3-methylcyclopentyl]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one;

4-[[1-cyclopropylethyl]amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(butylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(2-ethylbutyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(pentylamino)thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbutyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

4-[(3,3-dimethylbutyl)amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(2-methylbenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(4-methylbenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methylbut-2-enyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-(propylamino)thieno[3,2-

b]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-4-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-3-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(pyridin-2-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(3-methoxybenzyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(3-furylmethyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

3-({[6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-5-oxothieno[3,2-*b*]pyridin-4(5*H*)-yl]amino}methyl)benzonitrile;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(thien-3-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(cyclobutylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(benzylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-[(cyclohexylmethyl)amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(1,3-thiazol-5-ylmethyl)amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

4-[(3-bromobenzyl)amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(cyclohexylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(cyclopentylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-(cycloheptylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(1*R*,3*S*)-3-methylcyclohexyl]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[(1*R*,3*R*)-3-methylcyclohexyl]amino}thieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-[(1-ethylpropyl)amino]-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[1-phenylethyl]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

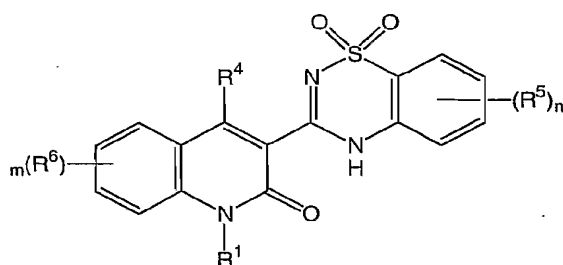
6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxy-4-[[*(1R)*-1-methylbutyl]amino]thieno[3,2-*b*]pyridin-5(4*H*)-one;

5 4-(cyclobutylamino)-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one;

4-[(cyclopropylmethyl)amino]-6-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-7-hydroxythieno[3,2-*b*]pyridin-5(4*H*)-one; and

10 2-({3-[4-(cyclohexylamino)-7-hydroxy-5-oxo-4,5-dihydrothieno[3,2-*b*]pyridin-6-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}oxy)acetamide.

15 The compound of claim 1 of formula (IV)



(IV)

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-, R_aR_bNC(O)NR_calkyl-, R_fR_gC=N- and R_kO-, wherein R¹ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_e), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_e), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_e;

R⁴ is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN-, N₃-, R_eS-, wherein R⁴ is substituted with 0, 1 or 2 substituents

independently selected from the group consisting of halo, nitro, cyano, -OH, -NH₂, and -COOH;

R⁵ is independently selected at each occurrence from the group consisting of alkenyl,
 5 alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo,
 haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl,
 hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-,
 R_a(O)₂S-, R_aR_bNalkyl-, R_a(O)SN(R_f)-, R_aSO₂N(R_f)-, R_a(O)SN(R_f)alkyl-, R_aSO₂N(R_f)alkyl-,
 R_aR_bNSO₂N(R_f)-, R_aR_bNSO₂N(R_f)alkyl-, R_aR_bNC(O)-, R_kOC(O)-, R_kOC(O)alkyl-,
 10 R_kOalkyl-, R_aR_bNSO₂-, R_aR_bNSO₂alkyl-, (R_bO)(R_a)P(O)O- and -OR_k, wherein each R⁵ is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl,
 heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c),
 -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and
 15 -C(O)NR_cR_d;

R⁶ is independently selected at each occurrence from the group consisting of alkyl,
 alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, heterocyclealkyl, -(alkyl)(OR_k), -(alkyl)(NR_aR_b), -SR_a, -S(O)R_a,
 20 -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b; wherein each R⁶ is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, -OR_a, -NR_aR_b, -SR_a,
 -SOR_a, -SO₂R_a, -C(O)OR_a, -C(O)NR_aR_b and -NC(O)R_a;

R_a and R_b, at each occurrence, are independently selected from the group consisting
 of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl,
 cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl,
 haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl,
 heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN-, R_kO-, R_kOalkyl-, R_cR_dNalkyl-,
 30 R_cR_dNC(O)alkyl-, R_cSO₂-, R_cSO₂alkyl-, R_cC(O)-, R_cC(O)alkyl-, R_cOC(O)-, R_cOC(O)alkyl-,
 R_cR_dNalkylC(O)-, R_cR_dNC(O)-, R_cR_dNC(O)Oalkyl-, R_cR_dNC(O)N(R_e)alkyl-, wherein R_a and
 R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c,
 35 -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

alternatively, R_a and R_b, together with the nitrogen atom to which they are attached

form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{alkylSO}_2\text{NR}_c\text{R}_d$, $-\text{alkylC}(\text{O})\text{NR}_c\text{R}_d$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-\text{NR}_f\text{R}_h$, $-\text{OR}_f$, $-\text{CO}(\text{R}_f)$, $-\text{SR}_f$, $-\text{SOR}_f$, $-\text{SO}_2\text{R}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{OR}_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{N}(\text{H})\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{N}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{alkylN}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, and $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$,

-SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂,
 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl),
 -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

5 alternatively, R_f and R_g together with the carbon atom to which they are attached form
 a three- to seven-membered ring selected from the group consisting of cycloalkyl,
 cycloalkenyl and heterocycle;

10 alternatively, R_f and R_h together with the nitrogen atom to which they are attached
 form a three- to seven-membered ring selected from the group consisting of heterocycle and
 heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with
 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl,
 alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle,
 heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
 15 -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl),
 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH,
 -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl,
 20 cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl,
 haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-,
 R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-,
 R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is
 substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of
 25 alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl,
 heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d),
 -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, 2, 3, or 4; and

30

n is 0, 1, 2, 3, or 4;

with the proviso that when R⁴ is alkoxy, aryloxy, hydroxy or R_eS-, and R⁵ is
 hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl,
 35 cyano, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-, R_a(O)₂S-, R_aSO₂N(R_f)-, R_aR_bNC(O)-,
 R_kOC(O)-, R_aR_bNSO₂- or -OR_k, and R⁶ is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano,
 nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a,

-C(O)OR_a and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

- 5 16. The compound of claim 15 wherein R⁴ is hydroxy.
17. The compound of claim 16 wherein R¹ is selected from the group consisting of R_aR_bN-, R_cR_gC=N⁻ and R_kO-.
- 10 18. The compound of claim 15 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1E)-phenylmethylene]amino)-2(1H)-quinolinone;
 - 1-amino-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2(1H)-quinolinone;
 - 15 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-propoxyquinolin-2(1H)-one;
 - 1-(benzylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one;
 - 20 1-amino-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one;
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1-propylbutyl)amino]quinolin-2(1H)-one;
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;
 - 25 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(1-ethylpropyl)amino]-4-hydroxyquinolin-2(1H)-one;
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(pentylamino)quinolin-2(1H)-one;
 - 30 1-(cyclohexylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one;
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(2-methyl-1,3-thiazol-4-yl)methyl]amino]quinolin-2(1H)-one;
 - 3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isopropylamino)quinolin-2(1H)-one;
 - 35 1-(cyclobutylamino)-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1H)-one;

1-(cyclopentylamino)-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-methylcyclopentyl]amino)quinolin-2(1*H*)-one;

5 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(tetrahydro-2*H*-pyran-4-ylamino)quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-([1-ethylbutyl]amino)-4-hydroxyquinolin-2(1*H*)-one;

10 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3*R*)-3-methylcyclohexyl]amino)quinolin-2(1*H*)-one;

1-(cycloheptylamino)-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-([3-ethylcyclopentyl]amino)-4-hydroxyquinolin-2(1*H*)-one;

15 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-isopropylbutyl]amino)quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-phenylethyl]amino)quinolin-2(1*H*)-one;

20 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([1-thien-3-ylethyl]amino)quinolin-2(1*H*)-one;

1-([3,5-dimethylcyclohexyl]amino)-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-isopropylcyclohexyl)amino]quinolin-2(1*H*)-one;

25 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[1,2,3,4-tetrahydronaphthalen-2-ylamino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-(trifluoromethyl)cyclohexyl]amino)quinolin-2(1*H*)-one;

30 1-(butylamino)-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-([3-methylbutyl]amino)quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-[(3-furylmethyl)amino]-4-hydroxyquinolin-2(1*H*)-one;

35 3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-[(2-furylmethyl)amino]-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(thien-2-

ylmethyl)amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(1,3-thiazol-2-ylmethyl)amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-1-{[(2*R*)-2-ethyl-3-methylbutyl]amino}-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methylbenzyl)amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylbenzyl)amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(2-methylbenzyl)amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(3-methylthien-2-yl)methyl]amino]quinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(4-methoxybenzyl)amino]quinolin-2(1*H*)-one;

1-{[(5-chlorothien-2-yl)methyl]amino}-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

1-{[(2-chloro-1,3-thiazol-5-yl)methyl]amino}-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

1-[(3-bromobenzyl)amino]-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

1-[(4-bromobenzyl)amino]-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

1-[(2-bromobenzyl)amino]-3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxyquinolin-2(1*H*)-one;

3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-[(pyridin-3-ylmethyl)amino]quinolin-2(1*H*)-one;

3-({[3-(1,1-dioxido-4*H*-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2-oxoquinolin-1(2*H*)-yl]amino}methyl)benzonitrile;

2-({3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

2-({3-[1-(cyclopentylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

2-({3-[1-(cyclohexylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-1,2,4-benzothiadiazin-7-yl)oxy]acetamide;

2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2-benzothiazin-7-yl}oxy)acetamide;

2-({3-[1-(butylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

5 2-[(3-[4-hydroxy-1-[(3-methylbutyl)amino]-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetamide;

3-(8-amino-7-hydroxy-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

10 2-({8-amino-3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

2-({3-[4-hydroxy-2-oxo-1-(propylamino)-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)acetamide;

2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)propanamide;

15 2-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)butanamide;

8-amino-3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl methanesulfonate;

20 1-[(cyclopropylmethyl)amino]-4-hydroxy-3-(7-hydroxy-8-nitro-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)quinolin-2(1H)-one;

3-(7-{2-[(3S)-3-aminopyrrolidin-1-yl]-2-oxoethoxy}-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one;

2-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]-N-ethylacetamide;

25 [(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetic acid;

3-{7-[2-(3-aminopyrrolidin-1-yl)-2-oxoethoxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one;

30 [(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one;

2-[(8-amino-3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetamide;

[(8-amino-3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)oxy]acetonitrile;

35 1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(2-hydroxyethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]quinolin-2(1H)-one;

1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(1H-imidazol-2-ylmethoxy)-1,1-

dioxido-4H-1,2,4-benzothiadiazin-3-yl]quinolin-2(1H)-one;

1-[(cyclopropylmethyl)amino]-3-[1,1-dioxido-7-(1,3-thiazol-2-ylmethoxy)-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one;

1-[(cyclopropylmethyl)amino]-3-[7-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one;

2-[[3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]oxy]methyl]-1,3-thiazole-4-carbonitrile;

3-[7-(2-aminoethoxy)-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl]-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one;

N-{2-[[3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]oxy]ethyl}methanesulfonamide;

3-{7-[(5-bromopyridin-2-yl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

4-hydroxy-1-(isobutylamino)-3-{7-[(3-nitropyridin-2-yl)oxy]-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl}quinolin-2(1H)-one;

tert-butyl 3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-ylcarbamate;

3-(7-amino-1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-[(cyclopropylmethyl)amino]-4-hydroxyquinolin-2(1H)-one;

methyl 2-chloro-6-({3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}oxy)isonicotinate;

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide;

N-(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide;

N-(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl}-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl)methanesulfonamide;

2-[[3-(1-amino-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]oxy]acetamide;

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}ethanesulfonamide;

benzyl 3-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}diazathiane-1-carboxylate 2,2-dioxide;

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}-N'-methylsulfamide; and

N-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}sulfamide.

19. The compound of claim 1 wherein:

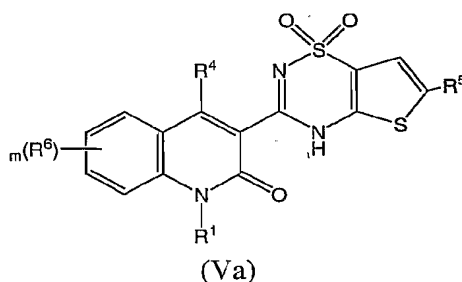
A is heteroaryl; and

5 R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of phenyl, pyridyl, pyrimidinyl, pyridazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, tetrazolyl, cyclopentyl and cyclohexyl.

20. The compound of claim 19 wherein A is thienyl.

21. The compound of claim 20 wherein R^2 and R^3 together with the carbon atoms to which they are attached form a phenyl ring.

22. The compound of claim 1 of formula (Va)



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

20 R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

30

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo,

hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

5 R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$,
 10 $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$,
 15 $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 20 arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

25 R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl,
 30 heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$, $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 35 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-alkylSO_2NR_cR_d$, $-alkylC(O)NR_cR_d$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-NR_fR_h$, $-OR_f$, $-CO(R_f)$, $-SR_f$, $-SOR_f$, $-SO_2R_f$, $-C(O)NR_fR_h$, $-SO_2NR_fR_h$, $-C(O)OR_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$, $-OR_f$, $-N(R_f)(R_h)$, $-C(O)R_f$, $-C(O)OR_f$, $-C(O)NR_fR_h$, $-C(O)N(H)NR_fR_h$, $-N(R_e)C(O)OR_f$, $-N(R_e)SO_2NR_fR_h$, $-N(R_e)C(O)NR_fR_h$, $-alkylN(R_e)C(O)OR_f$, $-alkylN(R_e)SO_2NR_fR_h$, and $-alkylN(R_e)C(O)NR_fR_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$, $-OR_f$, $-N(R_f)(R_h)$, $-C(O)R_f$, $-C(O)OR_f$ and $-C(O)NR_fR_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl,

heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl), -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂, -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

5

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

10

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle,

15

heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

20

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-, R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-, R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is

25

substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d; and

30

m is 0, 1, 2, 3, or 4;

with the proviso that when R⁴ is alkoxy, aryloxy, hydroxy or R_eS-, and R⁵ is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-, R_a(O)₂S-, R_aSO₂N(R_f)-, R_aR_bNC(O)-, R_kOC(O)-, R_aR_bNSO₂- or -OR_k, and R⁶ is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl,

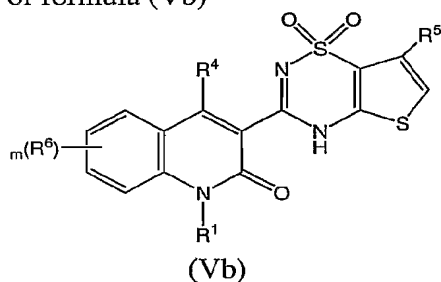
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arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

23. The compound of claim 22 wherein R^4 is hydroxy.

24. The compound of claim 23 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_fR_gC=N-$ and R_kO- .

25. The compound of claim 1 of formula (Vb)



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-$

COOH;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$, $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and

heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{alkylSO}_2\text{NR}_c\text{R}_d$,
 5 $-\text{alkylC}(\text{O})\text{NR}_c\text{R}_d$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-\text{NR}_f\text{R}_h$, $-\text{OR}_f$, $-\text{CO}(\text{R}_f)$, $-\text{SR}_f$, $-\text{SOR}_f$, $-\text{SO}_2\text{R}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{SO}_2\text{NR}_f\text{R}_h$,
 10 $-\text{C}(\text{O})\text{OR}_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 15 heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{N}(\text{H})\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{N}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{alkylN}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, and $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 25 heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 35 cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{alkyl}$, $-\text{alkyl}-\text{OH}$, $-\text{alkyl}-\text{O}-\text{alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylN}(\text{alkyl})_2$,

-alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-, R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-, R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d; and

m is 0, 1, 2, 3, or 4;

with the proviso that when R⁴ is hydroxy or R_eS-, and R⁵ is hydrogen, unsubstituted alkyl, halo or -OR_k, and R⁶ is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

26. The compound of claim 25 wherein R⁴ is hydroxy.

27. The compound of claim 26 wherein R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_fR_gC=N- and R_kO-.

28. The compound of claim 21 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:

N-({3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinoliny]-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl}methyl)urea;

1-benzyl-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl}quinolin-2(1*H*)-one;

1-Benzyl-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]quinolin-2(1*H*)-one;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxylic acid 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-(2-hydroxyethyl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-[(1*S*)-2-hydroxy-1-(aminocarbonyl)ethyl]-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

N-(2-amino-2-oxoethyl)-3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-[(1*S*)-2-hydroxy-1-methylethyl]-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N,N*-bis(2-hydroxyethyl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

1-benzyl-4-hydroxy-3-(7-{[(3*R*)-3-hydroxypyrrolidin-1-yl]carbonyl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl)quinolin-2(1*H*)-one;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-(3-hydroxypropyl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;

3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-*N*-[(2*S*)-2,3-

dihydroxypropyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-1-(hydroxymethyl)propyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[(1S)-1-(hydroxymethyl)-
 5 2-methylpropyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-hydroxybutyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-N-[2-hydroxy-2-(4-hydroxyphenyl)ethyl]-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 10 1-benzyl-3-[1,1-dioxido-7-(piperazin-1-ylcarbonyl)-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-4-hydroxyquinolin-2(1H)-one;
 N-[5-(aminocarbonyl)pyridin-2-yl]-3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-4H-thieno[2,3-e][1,2,4]thiadiazine-7-carboxamide 1,1-dioxide;
 [3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl carbamate;
 15 [3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl aminocarbonylcarbamate;
 3-[7-(azidomethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-1-benzyl-4-hydroxyquinolin-2(1H)-one;
 20 3-[7-(aminomethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]-1-benzyl-4-hydroxyquinolin-2(1H)-one;
 N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}methanesulfonamide;
 N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}nicotinamide;
 25 N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}morpholine-4-carboxamide;
 N-{[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl]methyl}-2-hydroxyacetamide;
 30 1-[(cyclopropylmethyl)amino]-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl}quinolin-2(1H)-one;
 1-[(cyclopropylmethyl)amino]-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-3-yl]quinolin-2(1H)-one;
 N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl)methyl]methanesulfonamide;
 35 N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4H-thieno[2,3-e][1,2,4]thiadiazin-7-yl)methyl]ethanesulfonamide;

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]propane-1-sulfonamide;

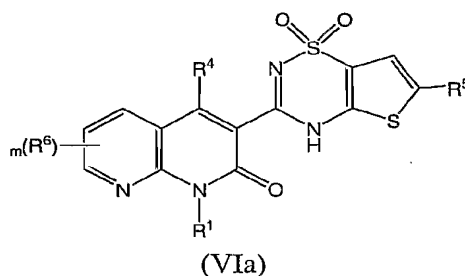
N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]propane-2-sulfonamide;

5 N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]benzenesulfonamide; and

N-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]-1-phenylmethanesulfonamide.

10 29. The compound of claim 20 wherein R² and R³, together with the carbon atoms to which they are attached form a pyridyl ring.

30. The compound of claim 1 of formula (VIa)



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-, R_aR_bNC(O)NR_calkyl-, R_fR_gC=N- and R_kO-, wherein R¹ is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_e), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_e), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_e;

R⁴ is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN-, N₃-, R_eS-, wherein R⁴ is substituted with 0, 1 or 2 substituents

independently selected from the group consisting of halo, nitro, cyano, -OH, -NH₂, and -COOH;

R⁵ is independently selected at each occurrence from the group consisting of alkenyl,
 5 alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo,
 haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl,
 hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-,
 R_a(O)₂S-, R_aR_bNalkyl-, R_a(O)SN(R_f)-, R_aSO₂N(R_f)-, R_a(O)SN(R_f)alkyl-, R_aSO₂N(R_f)alkyl-,
 R_aR_bNSO₂N(R_f)-, R_aR_bNSO₂N(R_f)alkyl-, R_aR_bNC(O)-, R_kOC(O)-, R_kOC(O)alkyl-,
 10 R_kOalkyl-, R_aR_bNSO₂-, R_aR_bNSO₂alkyl-, (R_bO)(R_a)P(O)O- and -OR_k, wherein each R⁵ is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl,
 heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c),
 -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and
 15 -C(O)NR_cR_d;

R⁶ is independently selected at each occurrence from the group consisting of alkyl,
 alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, heterocyclealkyl, -(alkyl)(OR_k), -(alkyl)(NR_aR_b), -SR_a, -S(O)R_a,
 20 -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b; wherein each R⁶ is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, -OR_a, -NR_aR_b, -SR_a,
 -SOR_a, -SO₂R_a, -C(O)OR_a, -C(O)NR_aR_b and -NC(O)R_a;

R_a and R_b, at each occurrence, are independently selected from the group consisting
 of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl,
 cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl,
 haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl,
 heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN-, R_kO-, R_kOalkyl-, R_cR_dNalkyl-,
 30 R_cR_dNC(O)alkyl-, R_cSO₂-, R_cSO₂alkyl-, R_cC(O)-, R_cC(O)alkyl-, R_cOC(O)-, R_cOC(O)alkyl-,
 R_cR_dNalkylC(O)-, R_cR_dNC(O)-, R_cR_dNC(O)Oalkyl-, R_cR_dNC(O)N(R_e)alkyl-, wherein R_a and
 R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c,
 35 -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

alternatively, R_a and R_b, together with the nitrogen atom to which they are attached

form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -alkylSO₂NR_cR_d, -alkylC(O)NR_cR_d, -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R_c and R_d, at each occurrence, are independently selected from the group consisting of hydrogen, -NR_fR_h, -OR_f, -CO(R_f), -SR_f, -SOR_f, -SO₂R_f, -C(O)NR_fR_h, -SO₂NR_fR_h, -C(O)OR_f, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_h, -C(O)N(H)NR_fR_h, -N(R_e)C(O)OR_f, -N(R_e)SO₂NR_fR_h, -N(R_e)C(O)NR_fR_h, -alkylN(R_e)C(O)OR_f, -alkylN(R_e)SO₂NR_fR_h, and -alkylN(R_e)C(O)NR_fR_h;

alternatively, R_c and R_d, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f and -C(O)NR_fR_h;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f, R_g and R_h, at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl),

-SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂,
 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl),
 -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

5 alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

10 alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
 15 -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-, R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-, R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of
 25 alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d; and

m is 0, 1, 2, 3, or 4;

30

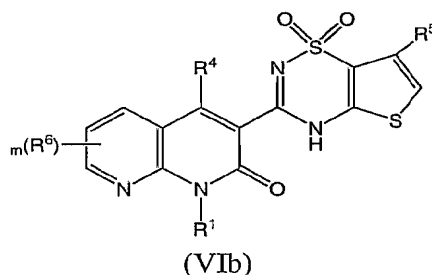
with the proviso that R⁴ is alkoxy, aryloxy, hydroxy or R_eS-, and R⁵ is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-, R_a(O)₂S-, R_aSO₂N(R_f)-, R_aR_bNC(O)-, R_kOC(O)-, R_aR_bNSO₂- or -OR_k, and R⁶ is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a
 35 and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl,

heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

31. The compound of claim 30 wherein R^4 is hydroxy.

32. The compound of claim 31 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkenylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, $R_aR_bN^-$, $R_aR_bNalkyl^-$, $R_aR_bNC(O)alkyl^-$, $R_fR_gC=N^-$ and R_kO^- .

33. The compound of claim 1 of formula (VIb)



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkenylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, $R_aR_bN^-$, $R_aR_bNalkyl^-$, $R_aR_bNC(O)alkyl^-$, $R_aR_bNC(O)Oalkyl^-$, $R_aR_bNC(O)NR_calkyl^-$, $R_fR_gC=N^-$ and R_kO^- , wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_c)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_c)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_c$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, $R_aR_bN^-$, N_3^- , R_eS^- , wherein R^4 is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-$

COOH;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$, $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and

heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{alkylSO}_2\text{NR}_c\text{R}_d$,
 5 $-\text{alkylC}(\text{O})\text{NR}_c\text{R}_d$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-\text{NR}_f\text{R}_h$, $-\text{OR}_f$, $-\text{CO}(\text{R}_f)$, $-\text{SR}_f$, $-\text{SOR}_f$, $-\text{SO}_2\text{R}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{SO}_2\text{NR}_f\text{R}_h$,
 10 $-\text{C}(\text{O})\text{OR}_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 15 heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{N}(\text{H})\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{N}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{alkylN}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, and $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 25 heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 35 cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{alkyl}$, $-\text{alkyl-OH}$, $-\text{alkyl-O-alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylN}(\text{alkyl})_2$,

-alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl),
-C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

alternatively, R_f and R_g together with the carbon atom to which they are attached form
5 a three- to seven-membered ring selected from the group consisting of cycloalkyl,
cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached
form a three- to seven-membered ring selected from the group consisting of heterocycle and
10 heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with
0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl,
alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle,
heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
-S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl),
15 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH,
-C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl,
cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl,
20 haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-,
R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-,
R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is
substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of
alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl,
25 heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d),
-SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d; and

m is 0, 1, 2, 3, or 4;

30 with the proviso that when R⁴ is hydroxy or R_eS-, and R⁵ is hydrogen, unsubstituted
alkyl, halo or -OR_k, and R⁶ is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl,
heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a
and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl,
cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl,
35 heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

34. The compound of claim 33 wherein R⁴ is hydroxy.

35. The compound of claim 34 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_fR_gC=N-$ and R_kO- .

36. The compound of claim 29 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:

1-butyl-4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl}-1,8-naphthyridin-2(1*H*)-one;

1-butyl-4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1,8-naphthyridin-2(1*H*)-one;

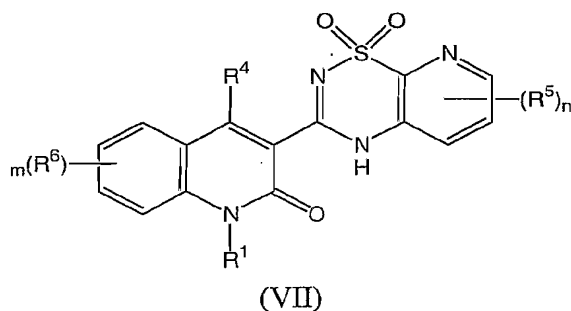
methyl 3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)-4*H*-thieno[2,3-*e*][1,2,4]thiadiazine-7-carboxylate 1,1-dioxide;

4-hydroxy-3-{7-[(methoxymethoxy)methyl]-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl}-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one; and

4-hydroxy-3-[7-(hydroxymethyl)-1,1-dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3-yl]-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one.

37. The compound of claim 19 wherein A is pyridyl.

38. The compound of claim 1 of formula (VII)



or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, alkylalkylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl,

carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$,
 5 $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

10 R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

15 R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$,
 20 $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl,
 25 heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

30 R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$,
 35 $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting

of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$,
 5 $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$,
 $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and
 R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$,
 10 $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached
 form a three- to six-membered ring selected from the group consisting of heteroaryl and
 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2
 15 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-alkylSO_2NR_cR_d$,
 $-alkylC(O)NR_cR_d$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and
 $-C(O)NR_cR_d$;

20 R_c and R_d , at each occurrence, are independently selected from the group consisting
 of hydrogen, $-NR_fR_h$, $-OR_f$, $-CO(R_f)$, $-SR_f$, $-SOR_f$, $-SO_2R_f$, $-C(O)NR_fR_h$, $-SO_2NR_fR_h$,
 $-C(O)OR_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl,
 cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and
 25 heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3
 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo,
 halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$,
 $-OR_f$, $-N(R_f)(R_h)$, $-C(O)R_f$, $-C(O)OR_f$, $-C(O)NR_fR_h$, $-C(O)N(H)NR_fR_h$, $-N(R_e)C(O)OR_f$,
 30 $-N(R_e)SO_2NR_fR_h$, $-N(R_e)C(O)NR_fR_h$, $-alkylN(R_e)C(O)OR_f$, $-alkylN(R_e)SO_2NR_fR_h$, and
 $-alkylN(R_e)C(O)NR_fR_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached
 form a three- to six-membered ring selected from the group consisting of heteroaryl and
 35 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2
 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,

heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

5

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{alkyl}$, $-\text{alkyl}-\text{OH}$, $-\text{alkyl}-\text{O}-\text{alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylN}(\text{alkyl})_2$, $-\text{alkylS}(\text{alkyl})$, $-\text{alkylS}(\text{O})(\text{alkyl})$, $-\text{alkylSO}_2\text{alkyl}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{alkyl})$, $-\text{C}(\text{O})\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{H})(\text{alkyl})$, and $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$;

10

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alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

20

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{alkyl}-\text{OH}$, $-\text{alkyl}-\text{O}-\text{alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylS}(\text{alkyl})$, $-\text{alkylS}(\text{O})(\text{alkyl})$, $-\text{alkylSO}_2\text{alkyl}$, $-\text{alkylN}(\text{alkyl})_2$, $-\text{N}(\text{H})\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{alkyl})$, $-\text{C}(\text{O})\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{H})(\text{alkyl})$, and $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$;

25

30

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, $\text{R}_a\text{R}_b\text{Nalkyl-}$, $\text{R}_a\text{Oalkyl-}$, $\text{R}_a\text{R}_b\text{NC}(\text{O})-$, $\text{R}_a\text{R}_b\text{NC}(\text{O})\text{alkyl}$, $\text{R}_a\text{S-}$, $\text{R}_a\text{S}(\text{O})-$, R_aSO_2- , $\text{R}_a\text{Salkyl-}$, $\text{R}_a(\text{O})\text{Salkyl-}$, $\text{R}_a\text{SO}_2\text{alkyl-}$, $\text{R}_a\text{OC}(\text{O})-$, $\text{R}_a\text{OC}(\text{O})\text{alkyl-}$, $\text{R}_a\text{C}(\text{O})-$, $\text{R}_a\text{C}(\text{O})\text{alkyl-}$, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl,

35

heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

m is 0, 1, 2, 3, or 4; and

5

n is 0, 1, 2, 3 or 4;

with the proviso that when R^4 is alkoxy, aryloxy, hydroxy or $\text{R}_c\text{S}-$, and R^5 is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, $\text{R}_a\text{R}_b\text{N}-$, $\text{R}_a\text{C}(\text{O})-$, $\text{R}_a\text{S}-$, $\text{R}_a(\text{O})\text{S}-$, $\text{R}_a(\text{O})_2\text{S}-$, $\text{R}_a\text{SO}_2\text{N}(\text{R}_f)-$, $\text{R}_a\text{R}_b\text{NC}(\text{O})-$, $\text{R}_k\text{OC}(\text{O})-$, $\text{R}_a\text{R}_b\text{NSO}_2-$ or $-\text{OR}_k$, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, $-\text{SR}_a$, $-\text{S}(\text{O})\text{R}_a$, $-\text{S}(\text{O})_2\text{R}_a$, $-\text{OR}_k$, $-\text{N}(\text{R}_a)(\text{R}_b)$, $-\text{C}(\text{O})\text{R}_a$, $-\text{C}(\text{O})\text{OR}_a$ and $-\text{C}(\text{O})\text{NR}_a\text{R}_b$, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl.

39. The compound of claim 38 wherein R^4 is hydroxy.

40. The compound of claim 39 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkenylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, $\text{R}_a\text{R}_b\text{N}-$, $\text{R}_a\text{R}_b\text{Nalkyl}-$, $\text{R}_a\text{R}_b\text{NC}(\text{O})\text{alkyl}-$, $\text{R}_f\text{R}_g\text{C}=\text{N}-$ and $\text{R}_k\text{O}-$.

25

41. The compound of claim 37 wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a pyridyl ring.

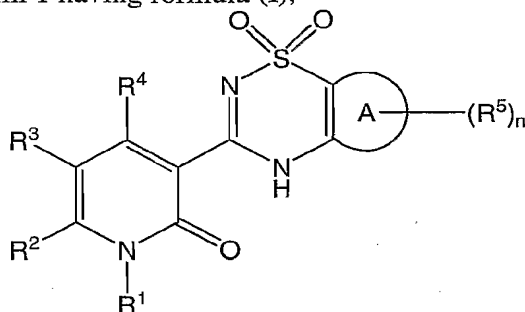
42. The compound of claim 41 wherein R^4 is hydroxy.

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43. The compound of claim 42 wherein R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkenylalkyl, alkyl, alkynyl, arylalkenyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, $\text{R}_a\text{R}_b\text{N}-$, $\text{R}_a\text{R}_b\text{Nalkyl}-$, $\text{R}_a\text{R}_b\text{NC}(\text{O})\text{alkyl}-$, $\text{R}_f\text{R}_g\text{C}=\text{N}-$ and $\text{R}_k\text{O}-$.

35

44. The compound of claim 1 having formula (I),



(I)

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

A is a monocyclic or bicyclic ring selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocycle;

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-, R_aR_bNC(O)NR_calkyl-, R_fR_gC=N- and R_kO-, wherein R¹ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_e), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_e), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_e;

R² and R³ are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, -N(R_a)(R_b), R_aR_bNC(O)-, -SR_a, -S(O)R_a, -S(O)₂R_a and R_aC(O)-; wherein R² and R³ are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a, alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, -(alkyl)(OR_k), -(alkyl)(NR_aR_b), -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b;

R⁴ is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN-, N₃-, R_eS-, wherein R⁴ is independently substituted with 0, 1 or 2

substituents independently selected from the group consisting of halo, nitro, cyano, -OH, -NH₂, and -COOH;

R⁵ is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN-, R_aC(O)-, R_aS-, R_a(O)S-, R_a(O)₂S-, R_aR_bNalkyl-, R_a(O)SN(R_f)-, R_aSO₂N(R_f)-, R_a(O)SN(R_f)alkyl-, R_aSO₂N(R_f)alkyl-, R_aR_bNSO₂N(R_f)-, R_aR_bNSO₂N(R_f)alkyl-, R_aR_bNC(O)-, R_kOC(O)-, R_kOC(O)alkyl-, R_kOalkyl-, R_aR_bNSO₂-, R_aR_bNSO₂alkyl-, (R_bO)(R_a)P(O)O- and -OR_k, wherein each R⁵ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R_a and R_b, at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN-, R_kO-, R_kOalkyl-, R_cR_dNalkyl-, R_cR_dNC(O)alkyl-, R_cSO₂-, R_cSO₂alkyl-, R_cC(O)-, R_cC(O)alkyl-, R_cOC(O)-, R_cOC(O)alkyl-, R_cR_dNalkylC(O)-, R_cR_dNC(O)-, R_cR_dNC(O)Oalkyl-, R_cR_dNC(O)N(R_e)alkyl-, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

alternatively, R_a and R_b, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -alkylSO₂NR_cR_d, -alkylC(O)NR_cR_d, -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-NR_fR_h$, $-OR_f$, $-CO(R_f)$, $-SR_f$, $-SOR_f$, $-SO_2R_f$, $-C(O)NR_fR_h$, $-SO_2NR_fR_h$, $-C(O)OR_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$, $-OR_f$, $-N(R_f)(R_h)$, $-C(O)R_f$, $-C(O)OR_f$, $-C(O)NR_fR_h$, $-C(O)N(H)NR_fR_h$, $-N(R_e)C(O)OR_f$, $-N(R_e)SO_2NR_fR_h$, $-N(R_e)C(O)NR_fR_h$, $-alkylN(R_e)C(O)OR_f$, $-alkylN(R_e)SO_2NR_fR_h$, and $-alkylN(R_e)C(O)NR_fR_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$, $-OR_f$, $-N(R_f)(R_h)$, $-C(O)R_f$, $-C(O)OR_f$ and $-C(O)NR_fR_h$;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-OH$, $-O(alkyl)$, $-NH_2$, $-N(H)(alkyl)$, $-N(alkyl)_2$, $-S(alkyl)$, $-S(O)(alkyl)$, $-SO_2alkyl$, $-alkyl-OH$, $-alkyl-O-alkyl$, $-alkylNH_2$, $-alkylN(H)(alkyl)$, $-alkylN(alkyl)_2$, $-alkylS(alkyl)$, $-alkylS(O)(alkyl)$, $-alkylSO_2alkyl$, $-N(H)C(O)NH_2$, $-C(O)OH$, $-C(O)O(alkyl)$, $-C(O)alkyl$, $-C(O)NH_2$, $-C(O)NH_2$, $-C(O)N(H)(alkyl)$, and $-C(O)N(alkyl)_2$;

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-, R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-, R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d; and

n is 0, 1, 2, 3, or 4.

45. The compound of claim 44 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-2(1H)-pyridinone;

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-2(1H)-pyridinone;

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-5-phenyl-2(1H)-pyridinone;

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-5,6-dimethyl-1-(3-methylbutyl)-2(1H)-pyridinone;

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-5,6-dimethyl-2(1H)-pyridinone;

1-benzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-phenyl-2(1H)-pyridinone;

1,5-dibenzyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-4-hydroxy-6-methyl-

2(1H)-pyridinone;

3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-1-(2-ethylbutyl)-4-hydroxy-6-methyl-5-phenyl-2(1H)-pyridinone;

1-butyl-3-(1,1-dioxido-4H-1,2,4-benzothiadiazin-3-yl)-2(1H)-pyridinone;

5 N-{3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydropyridin-3-yl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide;

N-[3-(1-benzyl-4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide;

10 N-[3-(4-hydroxy-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide;

N-[3-(4-hydroxy-1-isopentyl-5,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide;

benzyl 3-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]diazathiane-1-carboxylate 2,2-dioxide;

15 N-[3-(4-hydroxy-1-isopentyl-2-oxo-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]sulfamide;

N-{3-[1-(cyclobutylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-3-pyridinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide;

20 N-{3-[5-bromo-1-(cyclobutylmethyl)-4-hydroxy-2-oxo-1,2-dihydro-3-pyridinyl]-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl}methanesulfonamide; and

N-[3-(4-hydroxy-1-isopentyl-2-oxo-5-vinyl-1,2-dihydro-3-pyridinyl)-1,1-dioxido-4H-1,2,4-benzothiadiazin-7-yl]methanesulfonamide.

25 46. The compound of claim 1 wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a cycloalkyl ring.

47. The compound of claim 1 wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a five- or six-membered ring selected from the group consisting of thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, 30 oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, phenyl, pyridyl, pyridazinyl and pyrimidinyl; wherein said ring is optionally substituted with $(R^6)_m$; wherein

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, 35 $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$,

-SOR_a, -SO₂R_a, -C(O)OR_a, -C(O)NR_aR_b and -NC(O)R_a; and m is 0, 1, 2, 3 or 4.

48. The compound of claim 47 wherein R⁴ is hydroxy.

49. The compound of claim 1 wherein R⁴ is hydroxy, halo, -NH₂, -NH(alkyl), -N(alkyl)₂, -N(H)NH₂, -N₃, -N(H)(hydroxyalkyl), or R_cS-.

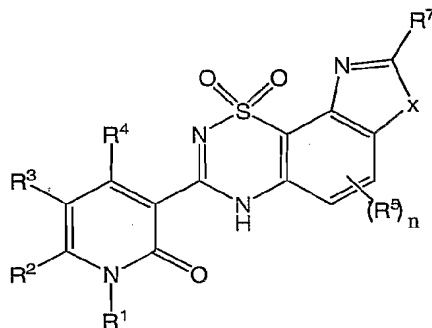
50. The compound of claim 1 wherein A is a bicyclic ring selected from the group consisting of heterocycle and heteroaryl.

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51. The compound of claim 50 wherein A is selected from the group consisting of naphthyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzoisothiazolyl, benzoisoxazolyl, benzoxazinyl, benzothiadiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl and naphthyridinyl, cinnolinyl and pteridinyl.

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52. The compound of claim 1 of formula (VIII)



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(VIII)

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

X is NH, N(alkyl), O or S.

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R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN-, R_aR_bNalkyl-, R_aR_bNC(O)alkyl-, R_aR_bNC(O)Oalkyl-,

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$R_a R_b NC(O)NR_c$ alkyl-, $R_f R_g C=N$ - and $R_k O$ -, wherein R^1 is substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_c R_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2 R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_c R_e$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxyacetyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, $-N(R_a)(R_b)$, $R_a R_b NC(O)-$, $-SR_a$, $-S(O)R_a$, $-S(O)_2 R_a$ and $R_a C(O)-$; wherein R^2 and R^3 are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a , alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_a R_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2 R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_a R_b$;

alternatively, R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, $R_a R_b N-$, N_3- , $R_c S-$, wherein R^4 is independently substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, $R_a R_b N-$, $R_a C(O)-$, $R_a S-$, $R_a(O)S-$, $R_a(O)_2 S-$, $R_a R_b Nalkyl-$, $R_a(O)SN(R_f)-$, $R_a SO_2 N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_a SO_2 N(R_f)alkyl-$, $R_a R_b NSO_2 N(R_f)-$, $R_a R_b NSO_2 N(R_f)alkyl-$, $R_a R_b NC(O)-$, $R_k OC(O)-$, $R_k OC(O)alkyl-$, $R_k Oalkyl-$, $R_a R_b NSO_2-$, $R_a R_b NSO_2 alkyl-$, $(R_b O)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_c R_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2 R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_c R_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is
 5 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R^7 is independently selected at each occurrence from the group consisting of alkenyl,
 10 alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$,
 15 $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^7 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and
 20 $-C(O)NR_cR_d$;

R_a and R_b , at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl,
 25 haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$, $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$, $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 30 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached
 35 form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,

oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{alkylSO}_2\text{NR}_c\text{R}_d$, $-\text{alkylC}(\text{O})\text{NR}_c\text{R}_d$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

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R_c and R_d , at each occurrence, are independently selected from the group consisting of hydrogen, $-\text{NR}_f\text{R}_h$, $-\text{OR}_f$, $-\text{CO}(\text{R}_f)$, $-\text{SR}_f$, $-\text{SOR}_f$, $-\text{SO}_2\text{R}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{OR}_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{N}(\text{H})\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{N}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{alkylN}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, and $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$;

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alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

R_c is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

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R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{SO}_2\text{alkyl}$, $-\text{alkyl-OH}$, $-\text{alkyl-O-alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylN}(\text{alkyl})_2$, $-\text{alkylS}(\text{alkyl})$, $-\text{alkylS}(\text{O})(\text{alkyl})$, $-\text{alkylSO}_2\text{alkyl}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{alkyl})$, $-\text{C}(\text{O})\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{H})(\text{alkyl})$, and $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$;

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bN alkyl-, R_aO alkyl-, $R_aR_bNC(O)$ -, $R_aR_bNC(O)$ alkyl, R_aS -, $R_aS(O)$ -, R_aSO_2 -, R_aS alkyl-, $R_a(O)$ Salkyl-, R_aSO_2 alkyl-, $R_aOC(O)$ -, $R_aOC(O)$ alkyl-, $R_aC(O)$ -, $R_aC(O)$ alkyl-, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, 2, 3, or 4; and

n is 0, 1 or 2.

53. The compound of claim 52 wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$.

54. The compound of claim 53 wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a five- or six-membered ring selected from the group consisting of phenyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazolyl, cyclopentyl, cyclohexyl and

thienyl.

55. The compound of claim 54 wherein R⁴ is hydroxy.

5 56. The compound of claim 55 or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof selected from the group consisting of:

3-(1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

10 3-[8-(chloromethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

3-{3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-8-yl}propanoic acid;

15 3-(8-{[(2-aminoethyl)amino]methyl}-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;
methyl {3-[4-hydroxy-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-8-yl} acetate;

4-hydroxy-3-(8-{[(3R)-3-hydroxypyrrolidin-1-yl]methyl}-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-1-(isobutylamino)quinolin-2(1H)-one;

20 3-[1,1-dioxido-8-(pyridinium-1-ylmethyl)-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-1-(isobutylamino)-2-oxo-1,2-dihydroquinolin-4-olate;

3-[1,1-dioxido-8-(pyrrolidin-1-ylmethyl)-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

3-[8-(3-aminophenyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

25 3-[8-(aminomethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

4-hydroxy-3-[8-(hydroxymethyl)-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl]-1-(isobutylamino)quinolin-2(1H)-one;

30 3-{8-[(butylamino)methyl]-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl}-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

3-[9-(butylamino)-1,1-dioxido-4H,8H-[1,4]oxazino[2,3-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(isobutylamino)quinolin-2(1H)-one;

4-hydroxy-1-(3-methylbutyl)-3-(8-methyl-1,1-dioxido-4H-[1,3]oxazolo[5,4-h][1,2,4]benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;

35 3-[1,1-dioxido-8-(trifluoromethyl)-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one;

4-hydroxy-3-(8-hydroxy-1,1-dioxido-4,7-dihydroimidazo[4,5-

h][1,2,4]benzothiadiazin-3-yl)-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one;
 4-hydroxy-1-(3-methylbutyl)-3-(8-methyl-1,1-dioxido-4,7-dihydroimidazo[4,5-
 h][1,2,4]benzothiadiazin-3-yl)-1,8-naphthyridin-2(1H)-one;
 3-[1,1-dioxido-8-(pentafluoroethyl)-4,7-dihydroimidazo[4,5-
 5 h][1,2,4]benzothiadiazin-3-yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one;
 3-[8-(chloromethyl)-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-
 yl]-4-hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one;
 {3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-1,1-
 dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-8-yl} acetonitrile;
 10 methyl {3-[4-hydroxy-1-(3-methylbutyl)-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]-
 1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-8-yl} acetate;
 3-(9,9-dioxido-6*H*-[1,2,5]thiadiazolo[3,4-*h*][1,2,4]benzothiadiazin-7-yl)-4-hydroxy-1-
 (3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one;
 3-(8-amino-1,1-dioxido-4,7-dihydroimidazo[4,5-h][1,2,4]benzothiadiazin-3-yl)-4-
 15 hydroxy-1-(3-methylbutyl)-1,8-naphthyridin-2(1H)-one; and
 4-hydroxy-3-[8-(hydroxymethyl)-1,1-dioxido-4,9-dihydroimidazo[4,5-
h][1,2,4]benzothiadiazin-3-yl]-1-(3-methylbutyl)-1,8-naphthyridin-2(1*H*)-one.

57. *N*-{3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl]-1,1-dioxido-4*H*-
 20 1,2,4-benzothiadiazin-7-yl}methanesulfonamide, or a pharmaceutically acceptable salt,
 stereoisomer or tautomer thereof.

58. *N*-[(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl}-1,1-
 dioxido-4*H*-thieno[2,3-*e*][1,2,4]thiadiazin-7-yl)methyl]methanesulfonamide, or a
 25 pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

59. *N*-(3-{1-[(cyclopropylmethyl)amino]-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyll}-1,1-
 dioxido-4*H*-1,2,4-benzothiadiazin-7-yl)methanesulfonamide, or a pharmaceutically
 acceptable salt, stereoisomer or tautomer thereof.

60. *N*-(3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyll]-1,1-dioxido-4*H*-
 1,2,4-benzothiadiazin-7-yl)sulfamide, or a pharmaceutically acceptable salt, stereoisomer or
 tautomer thereof.

61. *N*-(3-[1-(cyclobutylamino)-4-hydroxy-2-oxo-1,2-dihydro-3-quinolinyll]-1,1-dioxido-4*H*-
 1,2,4-benzothiadiazin-7-yl)-*N*'-methylsulfamide, or a pharmaceutically acceptable salt,

stereoisomer or tautomer thereof.

62. A pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of any one of claims 1, 57, 58, 59, 60 and 61, and a
5 pharmaceutically acceptable carrier.

63. The pharmaceutical composition of claim 62 further comprising one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or combination thereof.
10

64. The pharmaceutical composition of claim 63 wherein the host immune modulator is selected from the group consisting of interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine and a vaccine comprising an antigen and an adjuvant.
15

65. The pharmaceutical composition of claim 63 wherein the second antiviral agent inhibits replication of HCV by inhibiting host cellular functions associated with viral replication.

66. The pharmaceutical composition of claim 63 wherein the second antiviral agent inhibits
20 the replication of HCV by targeting proteins of the viral genome.

67. The pharmaceutical composition of claim 62 further comprising an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of liver.
25

68. The pharmaceutical composition of claim 62 further comprising one or more agents that treat patients for disease caused by hepatitis B (HBV) infection.

69. The pharmaceutical composition of claim 68 wherein the agent that treats patients for
30 disease caused by hepatitis B (HBV) infection is selected from the group consisting of L-deoxythymidine, adefovir, lamivudine and tenfovir.

70. The pharmaceutical composition of claim 62 further comprising one or more agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection.
35

71. The pharmaceutical composition of claim 70 wherein the agent that treats patients for disease caused by human immunodeficiency virus (HIV) infection is selected from the group

consisting of ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) and T-1249, or any combination thereof.

5

72. A method of treating or preventing infection caused by an RNA-containing virus comprising administering to a patient in need of such treatment a pharmaceutical composition of any one of claims 62, 63, 64, 65, 66, 67, 68, 69, 70 and 71.

10

73. A method of inhibiting the replication of an RNA-containing virus comprising contacting said virus with a therapeutically effective amount of a compound or combination of compounds of any one of claims 1, 57, 58, 59, 60 and 61.

15

74. A method of treating or preventing infection caused by an RNA-containing virus comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of any one of claims 1, 57, 58, 59, 60 and 61.

20

75. The method of claim 72 wherein the RNA-containing virus is hepatitis C virus.

76. The method of claim 75 further comprising the step of co-administering one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof.

25

77. The method of claim 76 wherein the host immune modulator is selected from the group consisting of interferon-alpha, pegylated-interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine and a vaccine comprising an antigen and an adjuvant.

30

78. The method of claim 76 wherein the second antiviral agent inhibits replication of HCV by inhibiting host cellular functions associated with viral replication.

79. The method of claim 76 wherein the second antiviral agent inhibits the replication of HCV by targeting proteins of the viral genome.

35

80. The method of claim 75 further comprising the step of co-administering an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver.

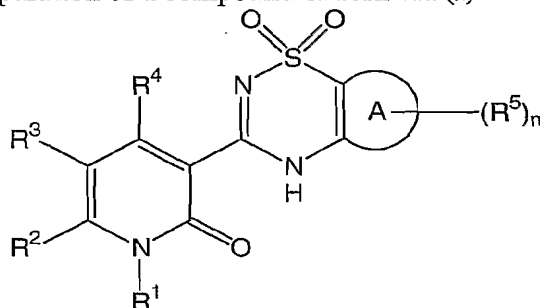
81. The method of claim 75 further comprising the step of co-administering one or more agents that treat patients for disease caused by hepatitis B (HBV) infection.

5 82. The method of claim 81 wherein the agent that treats patients for disease caused by hepatitis B (HBV) infection is selected from the group consisting of L-deoxythymidine, adefovir, lamivudine and tenfovir, or any combination thereof.

83. The method of claim 75 further comprising the step of co-administering one or more
10 agents that treat patients for disease caused by human immunodeficiency virus (HIV) infection.

84. The method of claim 83 wherein the agent that treats patients for disease caused by human immunodeficiency virus (HIV) infection is selected from the group consisting of
15 ritonavir, lopinavir, indinavir, nelfinavir, saquinavir, amprenavir, atazanavir, tipranavir, TMC-114, fosamprenavir, zidovudine, lamivudine, didanosine, stavudine, tenofovir, zalcitabine, abacavir, efavirenz, nevirapine, delavirdine, TMC-125, L-870812, S-1360, enfuvirtide (T-20) and T-1249, or any combination thereof.

20 85. A process for the preparation of a compound of formula (I)

 $(\mathbb{I},$

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

25 A is a monocyclic or bicyclic ring selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocycle;

R¹ is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, 30 alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl,

(cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxyacetyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, $-N(R_a)(R_b)$, $R_aR_bNC(O)-$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$ and $R_aC(O)-$; wherein R^2 and R^3 are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a , alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$;

alternatively, R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is independently substituted with 0, 1 or 2 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$, $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$, $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$, $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$,

-(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R⁶ is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, -(alkyl)(OR_k), -(alkyl)(NR_aR_b), -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b; wherein each R⁶ is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, -OR_a, -NR_aR_b, -SR_a, -SOR_a, -SO₂R_a, -C(O)OR_a, -C(O)NR_aR_b and -NC(O)R_a;

R_a and R_b, at each occurrence, are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN-, R_kO-, R_kOalkyl-, R_cR_dNalkyl-, R_cR_dNC(O)alkyl-, R_cSO₂-, R_cSO₂alkyl-, R_cC(O)-, R_cC(O)alkyl-, R_cOC(O)-, R_cOC(O)alkyl-, R_cR_dNalkylC(O)-, R_cR_dNC(O)-, R_cR_dNC(O)Oalkyl-, R_cR_dNC(O)N(R_e)alkyl-, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

alternatively, R_a and R_b, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -alkylSO₂NR_cR_d, -alkylC(O)NR_cR_d, -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

R_c and R_d, at each occurrence, are independently selected from the group consisting of hydrogen, -NR_fR_h, -OR_f, -CO(R_f), -SR_f, -SOR_f, -SO₂R_f, -C(O)NR_fR_h, -SO₂NR_fR_h, -C(O)OR_f, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3

substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$, $-\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{C}(\text{O})\text{N}(\text{H})\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$,
 5 $-\text{N}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, $-\text{N}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$, $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{OR}_f$, $-\text{alkylN}(\text{R}_e)\text{SO}_2\text{NR}_f\text{R}_h$, and $-\text{alkylN}(\text{R}_e)\text{C}(\text{O})\text{NR}_f\text{R}_h$;

alternatively, R_c and R_d , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and
 10 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_f)$, $-(\text{alkyl})(\text{NR}_f\text{R}_h)$, $-\text{SR}_f$, $-\text{S}(\text{O})\text{R}_f$, $-\text{S}(\text{O})_2\text{R}_f$, $-\text{OR}_f$, $-\text{N}(\text{R}_f)(\text{R}_h)$, $-\text{C}(\text{O})\text{R}_f$, $-\text{C}(\text{O})\text{OR}_f$ and $-\text{C}(\text{O})\text{NR}_f\text{R}_h$;

15

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f , R_g and R_h , at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and
 20 heteroarylalkyl; wherein each R_f , R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$,
 25 $-\text{SO}_2\text{alkyl}$, $-\text{alkyl}-\text{OH}$, $-\text{alkyl}-\text{O}-\text{alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylN}(\text{alkyl})_2$, $-\text{alkylS}(\text{alkyl})$, $-\text{alkylS}(\text{O})(\text{alkyl})$, $-\text{alkylSO}_2\text{alkyl}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{alkyl})$, $-\text{C}(\text{O})\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{H})(\text{alkyl})$, and $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$;

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;
 30

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and
 35 heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle,

heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
-S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl),
-alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH,
-C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

5

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl,
cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl,
haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, R_aR_bNalkyl-,
R_aOalkyl-, R_aR_bNC(O)-, R_aR_bNC(O)alkyl, R_aS-, R_aS(O)-, R_aSO₂-, R_aSalkyl-, R_a(O)Salkyl-,
10 R_aSO₂alkyl-, R_aOC(O)-, R_aOC(O)alkyl-, R_aC(O)-, R_aC(O)alkyl-, wherein each R_k is
substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of
alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl,
heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d),
-SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

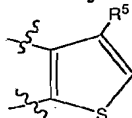
15

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, 3, or 4;

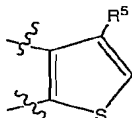
20

with the proviso that when A is a monocyclic ring other than



and R⁴ is alkoxy, aryloxy, hydroxy or R_cS-, and R⁵ is hydrogen, alkenyl, alkoxy, alkyl,
alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, R_aR_bN-, R_aC(O)-,
25 R_aS-, R_a(O)S-, R_a(O)₂S-, R_aSO₂N(R_i)-, R_aR_bNC(O)-, R_kOC(O)-, R_aR_bNSO₂- or -OR_k, and R⁶
is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl,
-SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R¹ is
not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl,
(cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl,
30 heterocyclealkenyl or heterocyclealkyl;

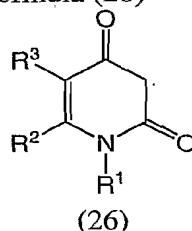
and with the further proviso that when A is



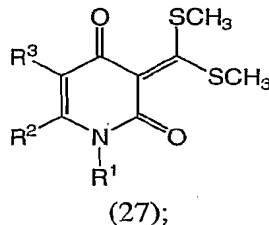
and R^4 is hydroxy or R_eS- , and R^5 is hydrogen, unsubstituted alkyl, halo or $-OR_k$, and R^6 is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$, then R^1 is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl;

comprising:

(a) contacting a compound of formula (26)

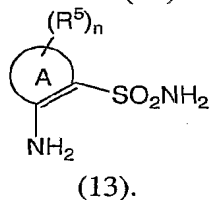


with carbon disulfide and a methylating agent in the presence of a base to provide a compound of formula (27)

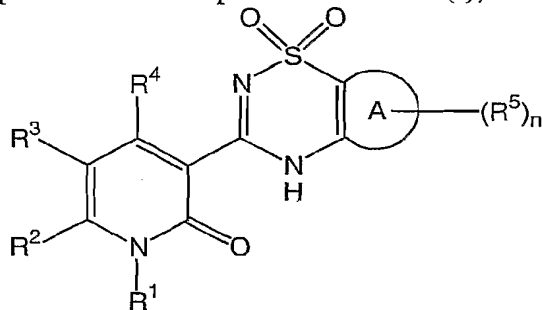


and

(b) contacting the compound of formula (27) with a compound of formula (13)



86. A process for the preparation of a compound of formula (I),



(I)

or a pharmaceutically acceptable salt form, stereoisomer or tautomer thereof, wherein:

A is a monocyclic or bicyclic ring selected from the group consisting of aryl,
5 cycloalkyl, cycloalkenyl, heteroaryl and heterocycle;

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyacetylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl,
10 carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is independently substituted with 0,
15 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxyacetylalkyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, $-N(R_a)(R_b)$, $R_aR_bNC(O)-$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$ and $R_aC(O)-$;
20 wherein R^2 and R^3 are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a , alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$;

alternatively, R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl,
30 heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$;

R^4 is selected from the group consisting of alkoxy, arylalkoxy, aryloxy, halo, hydroxy, R_aR_bN- , N_3- , R_eS- , wherein R^4 is independently substituted with 0, 1 or 2
35 substituents independently selected from the group consisting of halo, nitro, cyano, $-OH$, $-NH_2$, and $-COOH$;

R^5 is independently selected at each occurrence from the group consisting of alkenyl, alkoxy, alkyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, azidoalkyl, formyl, halo, haloalkyl, halocarbonyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, hydroxyalkyl, cycloalkyl, cyano, cyanoalkyl, nitro, R_aR_bN- , $R_aC(O)-$, R_aS- , $R_a(O)S-$,
 5 $R_a(O)_2S-$, $R_aR_bNalkyl-$, $R_a(O)SN(R_f)-$, $R_aSO_2N(R_f)-$, $R_a(O)SN(R_f)alkyl-$, $R_aSO_2N(R_f)alkyl-$,
 $R_aR_bNSO_2N(R_f)-$, $R_aR_bNSO_2N(R_f)alkyl-$, $R_aR_bNC(O)-$, $R_kOC(O)-$, $R_kOC(O)alkyl-$,
 $R_kOalkyl-$, $R_aR_bNSO_2-$, $R_aR_bNSO_2alkyl-$, $(R_bO)(R_a)P(O)O-$ and $-OR_k$, wherein each R^5 is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl,
 10 heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$,
 $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and
 $-C(O)NR_cR_d$;

R^6 is independently selected at each occurrence from the group consisting of alkyl,
 15 alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$,
 $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is
 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group
 consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$,
 20 $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting
 of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl,
 cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl,
 25 haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl,
 heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN- , R_kO- , $R_kOalkyl-$, $R_cR_dNalkyl-$,
 $R_cR_dNC(O)alkyl-$, R_cSO_2- , $R_cSO_2alkyl-$, $R_cC(O)-$, $R_cC(O)alkyl-$, $R_cOC(O)-$, $R_cOC(O)alkyl-$,
 $R_cR_dNalkylC(O)-$, $R_cR_dNC(O)-$, $R_cR_dNC(O)Oalkyl-$, $R_cR_dNC(O)N(R_e)alkyl-$, wherein R_a and
 R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl,
 30 alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle,
 arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$,
 $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached
 35 form a three- to six-membered ring selected from the group consisting of heteroaryl and
 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2
 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,

oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -alkylSO₂NR_cR_d, -alkylC(O)NR_cR_d, -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

5

R_c and R_d, at each occurrence, are independently selected from the group consisting of hydrogen, -NR_fR_h, -OR_f, -CO(R_f), -SR_f, -SOR_f, -SO₂R_f, -C(O)NR_fR_h, -SO₂NR_fR_h, -C(O)OR_f, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_h, -C(O)N(H)NR_fR_h, -N(R_e)C(O)OR_f, -N(R_e)SO₂NR_fR_h, -N(R_e)C(O)NR_fR_h, -alkylN(R_e)C(O)OR_f, -alkylN(R_e)SO₂NR_fR_h, and -alkylN(R_e)C(O)NR_fR_h;

10

15

alternatively, R_c and R_d, together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f, -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f and -C(O)NR_fR_h;

25

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

R_f, R_g and R_h, at each occurrence, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl), -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂, -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

30

35

alternatively, R_f and R_g together with the carbon atom to which they are attached form a three- to seven-membered ring selected from the group consisting of cycloalkyl, cycloalkenyl and heterocycle;

5

alternatively, R_f and R_h together with the nitrogen atom to which they are attached form a three- to seven-membered ring selected from the group consisting of heterocycle and heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl, heteroarylalkyl, $-\text{OH}$, $-\text{O}(\text{alkyl})$, $-\text{NH}_2$, $-\text{N}(\text{H})(\text{alkyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{alkyl})$, $-\text{S}(\text{O})(\text{alkyl})$, $-\text{alkyl}-\text{OH}$, $-\text{alkyl}-\text{O}-\text{alkyl}$, $-\text{alkylNH}_2$, $-\text{alkylN}(\text{H})(\text{alkyl})$, $-\text{alkylS}(\text{alkyl})$, $-\text{alkylS}(\text{O})(\text{alkyl})$, $-\text{alkylSO}_2\text{alkyl}$, $-\text{alkylN}(\text{alkyl})_2$, $-\text{N}(\text{H})\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{alkyl})$, $-\text{C}(\text{O})\text{alkyl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{N}(\text{H})(\text{alkyl})$, and $-\text{C}(\text{O})\text{N}(\text{alkyl})_2$;

15

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, $R_aR_b\text{Nalkyl-}$, $R_a\text{Oalkyl-}$, $R_aR_b\text{NC}(\text{O})-$, $R_aR_b\text{NC}(\text{O})\text{alkyl}$, $R_a\text{S-}$, $R_a\text{S}(\text{O})-$, $R_a\text{SO}_2-$, $R_a\text{Salkyl-}$, $R_a(\text{O})\text{Salkyl-}$, $R_a\text{SO}_2\text{alkyl-}$, $R_a\text{OC}(\text{O})-$, $R_a\text{OC}(\text{O})\text{alkyl-}$, $R_a\text{C}(\text{O})-$, $R_a\text{C}(\text{O})\text{alkyl-}$, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(\text{alkyl})(\text{OR}_c)$, $-(\text{alkyl})(\text{NR}_c\text{R}_d)$, $-\text{SR}_c$, $-\text{S}(\text{O})\text{R}_c$, $-\text{S}(\text{O})_2\text{R}_c$, $-\text{OR}_c$, $-\text{N}(\text{R}_c)(\text{R}_d)$, $-\text{C}(\text{O})\text{R}_c$, $-\text{C}(\text{O})\text{OR}_c$ and $-\text{C}(\text{O})\text{NR}_c\text{R}_d$;

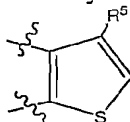
25

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, 3, or 4;

30

with the proviso that when A is a monocyclic ring other than



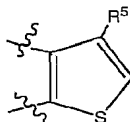
and R^4 is alkoxy, aryloxy, hydroxy or $\text{R}_e\text{S-}$, and R^5 is hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, halo, heteroaryl, heterocyclealkyl, cycloalkyl, cyano, nitro, $\text{R}_a\text{R}_b\text{N-}$, $\text{R}_a\text{C}(\text{O})-$, $\text{R}_a\text{S-}$, $\text{R}_a(\text{O})\text{S-}$, $\text{R}_a(\text{O})_2\text{S-}$, $\text{R}_a\text{SO}_2\text{N}(\text{R}_f)-$, $\text{R}_a\text{R}_b\text{NC}(\text{O})-$, $\text{R}_k\text{OC}(\text{O})-$, $\text{R}_a\text{R}_b\text{NSO}_2-$ or $-\text{OR}_k$, and R^6

35

is hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl,

5 heterocyclealkenyl or heterocyclealkyl;

and with the further proviso that when A is

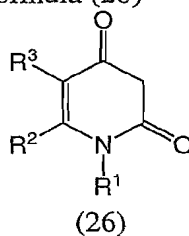


and R⁴ is hydroxy or R_eS-, and R⁵ is hydrogen, unsubstituted alkyl, halo or -OR_k, and R⁶ is
 10 hydrogen, alkyl, alkenyl, alkynyl, halo, cyano, nitro, aryl, heteroaryl, heterocyclealkyl, -SR_a, -S(O)R_a, -S(O)₂R_a, -OR_k, -N(R_a)(R_b), -C(O)R_a, -C(O)OR_a and -C(O)NR_aR_b, then R¹ is not hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocyclealkenyl or heterocyclealkyl;

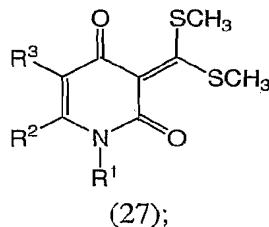
15

comprising:

(a) contacting a compound of formula (26)

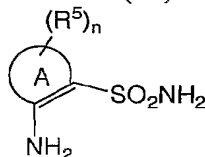


20 with tris(methylthio)methyl methyl sulfate in the presence of a base to provide a compound of formula (27)



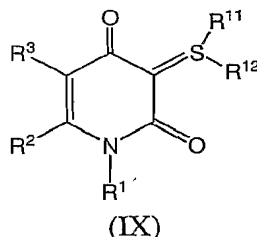
and

25 (b) contacting the compound of formula (27) with a compound of formula (13)



(13).

87. A compound having formula (IX),



or a pharmaceutically acceptable salt form, tautomer or stereoisomer thereof, wherein

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, alkylcarbonylalkyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylsulfanylalkyl, arylsulfonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, formylalkyl, haloalkoxyalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylsulfonylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkyl, nitroalkyl, R_aR_bN- , $R_aR_bNalkyl-$, $R_aR_bNC(O)alkyl-$, $R_aR_bNC(O)Oalkyl-$, $R_aR_bNC(O)NR_calkyl-$, $R_fR_gC=N-$ and R_kO- , wherein R^1 is independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_e)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_e)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_e$;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkylalkyl, alkyl, aryl, arylalkyl, heteroaryl, heterocycle, heteroarylalkyl, cyano, halo, $-N(R_a)(R_b)$, $R_aR_bNC(O)-$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$ and $R_aC(O)-$; wherein R^2 and R^3 are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of R_a , alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$;

alternatively, R^2 and R^3 , together with the carbon atoms to which they are attached form a five- or six-membered ring selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycle, wherein said aryl, cycloalkyl, heteroaryl and heterocycle is optionally substituted with $(R^6)_m$;

R^6 is independently selected at each occurrence from the group consisting of alkyl, alkenyl, alkynyl, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclealkyl, $-(alkyl)(OR_k)$, $-(alkyl)(NR_aR_b)$, $-SR_a$, $-S(O)R_a$, $-S(O)_2R_a$, $-OR_k$, $-N(R_a)(R_b)$, $-C(O)R_a$, $-C(O)OR_a$ and $-C(O)NR_aR_b$; wherein each R^6 is
 5 independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, haloalkyl, cyano, nitro, $-OR_a$, $-NR_aR_b$, $-SR_a$, $-SOR_a$, $-SO_2R_a$, $-C(O)OR_a$, $-C(O)NR_aR_b$ and $-NC(O)R_a$;

R_a and R_b , at each occurrence, are independently selected from the group consisting
 10 of hydrogen, alkenyl, alkyl, alkylsulfanylalkyl, aryl, arylalkenyl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocyclealkenyl, heterocyclealkyl, hydroxyalkylcarbonyl, nitroalkyl, R_cR_dN -, R_kO -, $R_kOalkyl$ -, $R_cR_dNalkyl$ -, $R_cR_dNC(O)alkyl$ -, R_cSO_2 -, R_cSO_2alkyl -, $R_cC(O)$ -, $R_cC(O)alkyl$ -, $R_cOC(O)$ -, $R_cOC(O)alkyl$ -,
 15 $R_cR_dNalkylC(O)$ -, $R_cR_dNC(O)$ -, $R_cR_dNC(O)Oalkyl$ -, $R_cR_dNC(O)N(R_e)alkyl$ -, wherein R_a and R_b are substituted with 0, 1 or 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

20

alternatively, R_a and R_b , together with the nitrogen atom to which they are attached form a three- to six-membered ring selected from the group consisting of heteroaryl and heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 25 oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_c)$, $-(alkyl)(NR_cR_d)$, $-alkylSO_2NR_cR_d$, $-alkylC(O)NR_cR_d$, $-SR_c$, $-S(O)R_c$, $-S(O)_2R_c$, $-OR_c$, $-N(R_c)(R_d)$, $-C(O)R_c$, $-C(O)OR_c$ and $-C(O)NR_cR_d$;

R_c and R_d , at each occurrence, are independently selected from the group consisting
 30 of hydrogen, $-NR_fR_h$, $-OR_f$, $-CO(R_f)$, $-SR_f$, $-SOR_f$, $-SO_2R_f$, $-C(O)NR_fR_h$, $-SO_2NR_fR_h$, $-C(O)OR_f$, alkenyl, alkyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, arylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl; wherein each R_c and R_d is independently substituted with 0, 1, 2, or 3
 35 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, $-(alkyl)(OR_f)$, $-(alkyl)(NR_fR_h)$, $-SR_f$, $-S(O)R_f$, $-S(O)_2R_f$,

-OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_h, -C(O)N(H)NR_fR_h, -N(R_e)C(O)OR_f,
 -N(R_e)SO₂NR_fR_h, -N(R_e)C(O)NR_fR_h, -alkylN(R_e)C(O)OR_f, -alkylN(R_e)SO₂NR_fR_h, and
 -alkylN(R_e)C(O)NR_fR_h;

5 alternatively, R_c and R_d, together with the nitrogen atom to which they are attached
 form a three- to six-membered ring selected from the group consisting of heteroaryl and
 heterocycle, wherein the heteroaryl and heterocycle are independently substituted with 0, 1, 2
 or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl,
 10 heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_f), -(alkyl)(NR_fR_h), -SR_f, -S(O)R_f, -S(O)₂R_f,
 -OR_f, -N(R_f)(R_h), -C(O)R_f, -C(O)OR_f and -C(O)NR_fR_h;

R_e is selected from the group consisting of hydrogen, alkenyl, alkyl and cycloalkyl;

15 R_f, R_g and R_h, at each occurrence, are independently selected from the group
 consisting of hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl,
 cycloalkenyl, cycloalkenylalkyl, heterocycle, heterocyclealkyl, heteroaryl and
 heteroarylalkyl; wherein each R_f, R_g and R_h is independently substituted with 0, 1, 2 or 3
 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl,
 20 cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle, heteroaryl,
 heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl), -S(O)(alkyl),
 -SO₂alkyl, -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl), -alkylN(alkyl)₂,
 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -N(H)C(O)NH₂, -C(O)OH, -C(O)O(alkyl),
 -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

25 alternatively, R_f and R_g together with the carbon atom to which they are attached form
 a three- to seven-membered ring selected from the group consisting of cycloalkyl,
 cycloalkenyl and heterocycle;

30 alternatively, R_f and R_h together with the nitrogen atom to which they are attached
 form a three- to seven-membered ring selected from the group consisting of heterocycle and
 heteroaryl; wherein each of the heterocycle and heteroaryl is independently substituted with
 0, 1, 2 or 3 substituents independently selected from the group consisting of alkyl, alkenyl,
 alkynyl, cyano, halo, oxo, nitro, aryl, arylalkyl, cycloalkyl, cycloalkenyl, heterocycle,
 35 heteroaryl, heteroarylalkyl, -OH, -O(alkyl), -NH₂, -N(H)(alkyl), -N(alkyl)₂, -S(alkyl),
 -S(alkyl), -S(O)(alkyl), -alkyl-OH, -alkyl-O-alkyl, -alkylNH₂, -alkylN(H)(alkyl),
 -alkylS(alkyl), -alkylS(O)(alkyl), -alkylSO₂alkyl, -alkylN(alkyl)₂, -N(H)C(O)NH₂, -C(O)OH,

-C(O)O(alkyl), -C(O)alkyl, -C(O)NH₂, -C(O)NH₂, -C(O)N(H)(alkyl), and -C(O)N(alkyl)₂;

R_k is selected from the group consisting of hydrogen, alkenyl, alkyl, aryl, arylalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, formylalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocyclealkyl, nitroalkyl, $R_aR_bNalkyl-$, $R_aOalkyl-$, $R_aR_bNC(O)-$, $R_aR_bNC(O)alkyl$, R_aS- , $R_aS(O)-$, R_aSO_2- , $R_aSalkyl-$, $R_a(O)Salkyl-$, $R_aSO_2alkyl-$, $R_aOC(O)-$, $R_aOC(O)alkyl-$, $R_aC(O)-$, $R_aC(O)alkyl-$, wherein each R_k is substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, halo, cyano, nitro, haloalkyl, haloalkoxy, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, alkoxyalkoxyalkyl, -(alkyl)(OR_c), -(alkyl)(NR_cR_d), -SR_c, -S(O)R_c, -S(O)₂R_c, -OR_c, -N(R_c)(R_d), -C(O)R_c, -C(O)OR_c and -C(O)NR_cR_d;

m is 0, 1, 2, 3, or 4; and

R^{11} and R^{12} are independently selected from the group consisting of alkyl, alkenyl and alkynyl.

88. The compound of claim 87, or a pharmaceutically acceptable salt form, tautomer or stereoisomer thereof selected from the group consisting of:

- 1-benzyl-3-(bis(methylthio)methylene)-1H-quinoline-2,4(1*H*,3*H*)-dione;
- 3-[bis(methylthio)methylene]-1-butyl-1,8-naphthyridine-2,4(1*H*,3*H*)-dione;
- 3-[bis(methylthio)methylene]-1-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)quinoline-2,4(1*H*,3*H*)-dione;
- 3-[bis(methylthio)methylene]-1-[(cyclopropylmethyl)amino]quinoline-2,4(1*H*,3*H*)-dione;
- 3-[bis(methylthio)methylene]-1-(3-methylbutyl)pyridine-2,4(1*H*,3*H*)-dione;
- 1-benzyl-3-[bis(methylthio)methylene]pyridine-2,4(1*H*,3*H*)-dione;
- 3-[bis(methylthio)methylene]-1-(cyclobutylamino)quinoline-2,4(1*H*,3*H*)-dione; and
- 3-[bis(methylthio)methylene]-1-(cyclobutylmethyl)pyridine-2,4(1*H*,3*H*)-dione.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/34707

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D513/04 C07D519/00 C07D495/04 C07D417/04
 C07D513/14 C07D417/14 A61K31/554 A61P31/00 C07D215/22
 C07D401/04 C07D213/69 //(C07D519/00,513:00,471:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 85172 A (SMITHKLINE BEECHAM) 15 November 2001 (2001-11-15) claims 1-4; examples 1,6,8 ----	1,72,75
P,X	WO 02 098424 A (SMITHKLINE BEECHAM) 12 December 2002 (2002-12-12) examples 2,10,18,20,33,50,51,60,70,71, 88,117,124, 128-131,134,140,152,153,170, 182-184,190,193,195-197,200,205; claims 1,15 ----	1,72,75
P,X	WO 03 059356 A (SMITHKLINE BEECHAM) 24 July 2003 (2003-07-24) claims 1,13,16; examples 17-21,23,26,27 -----	1,72,75

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 April 2004

Date of mailing of the international search report

19/04/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/34707

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 (C07D471/04, 239:00, 221:00), (C07D495/04, 333:00, 221:00),
(C07D513/04, 277:00, 221:00), (C07D513/04, 333:00, 285:00),
(C07D471/04, 237:00, 221:00), (C07D513/04, 285:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

2 April 2004

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/34707

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 72-84 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/34707

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0185172	A	15-11-2001	AU	6137701 A		20-11-2001
			EP	1292310 A1		19-03-2003
			WO	0185172 A1		15-11-2001
			US	2004034041 A1		19-02-2004
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WO 03059356	A	24-07-2003	WO	03059356 A2		24-07-2003
<hr/>						